VOLUME 61 *June 1950* NUMBER 6

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

An Evaluation of the Method of Quantitative Airborne Infection and its Use in the Study of the Pathogenesis of Tuberculosis. MAX B. LURIE, A. G. HEPPLESTON, SAMUEL ABRAMSON, AND IRENE B. SWARTZ 765
Extraction of Proteins and Other Constituents from the Tubercle Bacillus, with Some Observations on Their Chemical and Biological Properties. ROBERT J. HECKLY AND DENNIS W. WATSON 798
The Results of the Treatment of Active Minimal Pulmonary Tuberculosis with "Modified" Bed Rest. A Statistical Analysis of 289 Patients Followed for Seven Years after Discharge from Trudeau Sanatorium. ROGER S. MITCHELL AND JACK R. KNUDSON 809
Incidence and Significance of Thromboembolism in Pulmonary Tuberculosis. RUSSELL S. JONES, THOMAS C. BLACK, AND HAROLD A. SPARR 826
The Occurrence of Pulmonary Tuberculosis following Pulmonary Excision for Nontuberculous Diseases. HARRY L. KATZ 835
Pleural, Peritoneal, and Pericardial Tuberculosis: A Review of 209 Cases Uncomplicated by Treatment or Secondary Infection. OSCAR AUERBACH 845
Influence of *p*-(Di-n-Propylsulfamyl)-Benzoic Acid, "Benemid," on Para-aminosalicylic Acid (PAS) Plasma Concentrations. WILLIAM P. BOGER AND FORREST W. PITTS 862
Tuberculous Patients Two and a Half Years after Streptomycin Treatment. M. MAXIM STEINBACH, GEORGE C. LEINER, ABRAHAM A. POLACHEK, AND PAUL HELLER 868
Aureomycin in the Treatment of Tuberculosis. W. S. SCHWARTZ, S. T. WALTON, AND R. E. MOYER 875
Case Reports:
Tuberculous Infection with Streptomycin-resistant Organisms. L. S. ARANY AND W. G. LEWIS 881
Spontaneous Mediastinal Emphysema and Bilateral Spontaneous Pneumothoraces. BERNARD HYDE AND LEROY HYDE 883
Primary Coccidioidomycosis and Concomitant Tuberculosis. MARCEL KAHN 887
Editorial: Implications of Rapidly Effective Tuberculosis Therapy. FLOYD M. FELDMANN 892
Letters to the Editors: Serum Gamma-Globulins in Pulmonary Tuberculosis. MAURICE J. SMALL 893
Books 895
Index of Subjects and Authors 899
Index of Abstracts 105

Published Monthly at Mount Royal and Guilford Avenues. Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N. Y.

Copyright 1950, by the National Tuberculosis Association

PRINTED IN U. S. A.

THE AMERICAN REVIEW
OF
TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia, Pa.

MANAGING EDITOR
WALSH McDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D.C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, JR., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Baltimore, Md.
HERBERT C. MAIER, New York, N. Y.
WILLIAM P. SHEPARD, San Francisco, Calif.
C. EUGENE WOODRUFF, Northville, Mich.

HELEN W. MILLER
Editorial Secretary

NOTICE TO SUBSCRIBERS AND CONTRIBUTORS

THE AMERICAN REVIEW OF TUBERCULOSIS is published by the National Tuberculosis Association and issued monthly about the first of the month. THE AMERICAN REVIEW OF TUBERCULOSIS is the official journal of the American Trudeau Society. A volume includes six numbers and begins with the January and July numbers.

Subscription: The subscription price of the REVIEW is $10 for the calendar year. Checks should be made payable to Collier Platt, Treasurer.

Character of the Review: The REVIEW invites the submission of original manuscripts on any phase of tuberculosis, nontuberculous pulmonary diseases, and related subjects of interest.

MANUSCRIPTS

Contributors are requested to pay particular attention to the following rules governing the preparation of manuscripts. Failure to follow these rules is a frequent cause of delay in the publication of articles.

Manuscripts should be sent in duplicate to the office of the Managing Editor, Walsh McDermott, 1790 Broadway, New York 19, N. Y., mailed flat, and transmitted by first-class mail with postage for return if not acceptable. They should be in English, double-spaced, typewritten on one side of the page, with wide margins. Tabular data should not be included in the text but should be presented in separate tables with appropriate reference in the text. All case reports should be written in complete sentences. Authors should exercise particular care in the preparation, notation, and description of figures and tables. References should be in REVIEW style. Each table must be accompanied by a descriptive title, and a suitable legend must be provided for each figure. Drawings must be made with india ink and all lettering should be made with a stencil. The quality of the reproduction of a roentgenogram depends upon both the quality of the original picture and of the glossy print obtained from photographing that picture. If a contributor does not have facilities available, preparation of figures or reproduction of roentgenograms may be handled through the Review office. Under those circumstances, the contributor should supply a neat, properly proportioned, and suitably entitled drawing or the original roentgenogram, and will be expected to defray the cost of these services.

The publishers will not be responsible for manuscripts, illustrations, etc., lost in transit. In order to save expense for authors' corrections in proof, manuscript should be carefully revised by the author before submission.

Abstracts: Authors wishing to have abstracts of their papers appear in ABSTRACTS OF TUBERCULOSIS will facilitate their publication by sending concise abstracts or reprints to the Managing Editor.

Reprints: Fifty reprints without covers of articles will be furnished to authors free of charge when requested in advance. A table showing cost of additional reprints with an order blank is submitted with proofs to the authors.

Single Copies: The price of single copies of this number of THE AMERICAN REVIEW OF TUBERCULOSIS is one dollar postpaid.

Advertising: Rates will be furnished by THE AMERICAN REVIEW OF TUBERCULOSIS, 1790 Broadway, New York 19, N. Y. on request.

The Publishers reserve the right to decline any advertising submitted and to censor all copy. Acceptance of an advertisement does not constitute official endorsement of the product advertised.

Entered as second-class matter March 9, 1917, at the post office at Baltimore, Md., under the Act of August 24, 1912. Acceptance for mailing at special rate of postage provided for in section 1103, act of October 3, 1917. Authorized on July 2, 1918.

a **new**
antibacterial
agent...

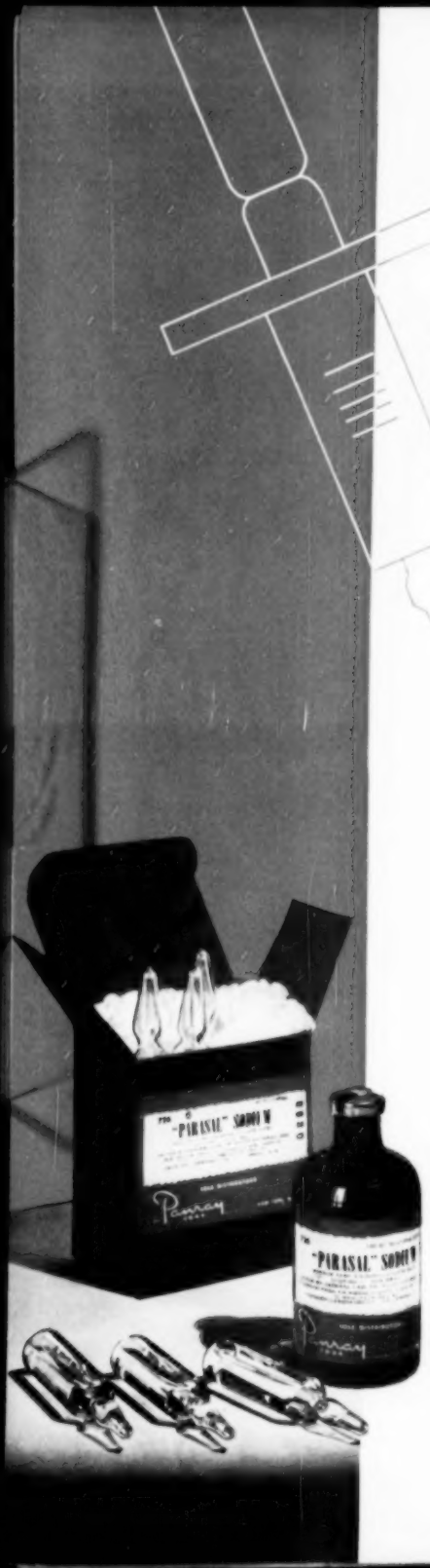
Wide antibacterial activity, low toxicity and virtual elimination of renal complications distinguish the use of Gantrisin* 'Roche', a new and remarkably soluble sulfonamide. Highly effective in urinary as well as systemic infections, Gantrisin does not require alkali therapy because it is soluble even in mildly acid urine. More than 20 articles in the recent literature attest its high therapeutic value and the low incidence of side-effects. Gantrisin is now available in 0.5 Gm tablets, as a syrup, and in ampuls. Additional information on request.

HOFFMANN-LA ROCHE INC. • NUTLEY 10 • N. J.

Gantrisin®

* *Brand of sulfisoxazole (3,4-dimethyl-5-sulfanilamido-isoxazole)*

'Roche'



In the chemotherapy of tuberculosis—
A New Form of PAS
for Clinical Investigation . . .

PARASAL SODIUM SOLUTION in VIALS and AMPULS

Sterile solutions of PARASAL SODIUM, Panray's brand of sodium para aminosalicylate, are now available to qualified investigators.

Packed under inert atmosphere to prevent decomposition, PARASAL SODIUM solution is water-white to pale yellow in color, an indication of its extreme purity. Each cc. of solution contains 20% of a special grade of PARASAL SODIUM, equivalent to exactly .174 gms. active PAS.

Ampuls of 10 cc.; multiple-dose vials of 100 cc.

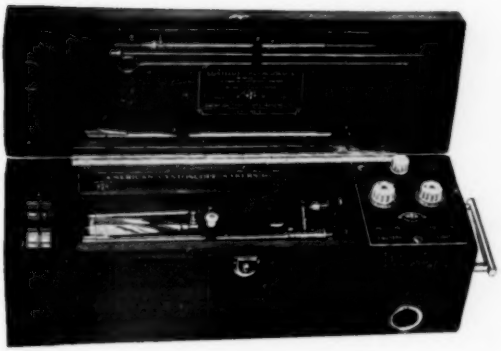
THE Panray CORP

CUSTOM MANUFACTURERS OF FINE MEDICINAL CHEMICALS

340 CANAL STREET, NEW YORK 13, N. Y.

The Coryllos Thoracoscope

WITH SELF-CONTAINED CAUTERY AND LIGHT TRANSFORMER



600A as illustrated with footswitch and cautery-light transformer. The biopsy forceps illustrated in lid of case is an accessory instrument and is sold separately.

Biopsy Forceps, Cat. No. 389

A sturdy portable instrument for the double cannula pneumonolysis technique, which adequately meets the requirements of the American surgeon. The Coryllos Thoracoscope consists of telescope, two cannulae, light carrier, two extra lamps and sterilizable lighting cord. The long and short cautery electrodes are equipped with ventilating shields which permit air circulation in the pleural cavity. The self-contained cautery and light transformer obviates the necessity of purchasing relatively expensive high-frequency generators and transformers. The instrument is contained in a polished, substantial walnut case with carrying handle. A space is provided for the footswitch which is included.

Supplementary instruments such as curved electrodes, flexible cannula, transilluminator and aspirating tube, biopsy specimen forceps, infiltration needle, etc. are also available for those who desire a more elaborate armamentarium.

Consult your Dealer or Write to us for Literature

WAPPLER A.C.M.I. TRADE MARK

AMERICAN CYSTOSCOPE MAKERS, INC.

1241 LAFAYETTE AVENUE, NEW YORK 59, N. Y.

When Dietary Supplementation

IS THE ORDER OF THE DAY

Many factors operate to prevent attainment of the high nutritional levels required in the successful treatment of tuberculosis: anorexia, gastrointestinal intolerance to foods, aversions to particular foods, and difficulty in mastication and deglutition. When such obstacles appear, the use of a dietary supplement can prove of real value, especially since the diet in tuberculosis is of great therapeutic importance.

The delicious food supplement made by mixing Ovaltine in milk can aid measurably in augmenting the daily intake of needed nutrients. As indicated in the table below, the recommended three glassfuls daily supply not only the very nutrients required in a dietary supplement, but also provide them in balanced generous amounts. Both plain and chocolate flavored Ovaltine are easily digested and delicious in taste. They are frequently accepted by the patient when many other foods are refused, hence are doubly valuable in attaining the desired nutritional levels.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk, provide:*

PROTEIN	32 Gm.	VITAMIN A	3000 I.U.
FAT	32 Gm.	VITAMIN B_1	1.16 mg.
CARBOHYDRATE	65 Gm.	RIBOFLAVIN	2.0 mg.
CALCIUM	1.12 Gm.	NIACIN	6.8 mg.
PHOSPHORUS	0.94 Gm	VITAMIN C	30.0 mg.
IRON	12 mg.	VITAMIN D	417 I.U.
COPPER	0.5 mg.	CALORIES	676

*Based on average reported values for milk.

Two kinds, Plain and Chocolate Flavored. Serving for serving, they are virtually identical in nutritional content.

NOW... a portable, fool-proof, long lasting

STORAGE BATTERY UNIT
for electrically lighted instruments

At long last, here is the powerful and dependable storage battery unit for lighting instruments that laryngologists, bronchoscopists and other physicians have dreamed about.

Just look at these features:

- **Contains two 4 volt, 6 ampere, portable, non-spill storage batteries.**
- **Two separately controlled circuits for lighting two separate instruments, when needed.**
- **Light and portable—only 16 lbs. complete.**
- **May be recharged with built-in charger by just plugging in the regular 110-115 volt, 60 cycle AC.**
- **You can regulate the brightness of your lights.**
- **Never a light failure with two storage batteries; one is always in reserve.**
- **Visible battery charge indicator tells when to recharge.**
- **Red bull's-eye warns of short circuit—or if light is burned out.**
- **True finger tip control for everything. No need to change instrument cord tips to different posts—just flip switch.**

These are just a few of the advantages. There are no moving parts—all wires and connections are color coded for simple operation. And if the cost is pro-rated over a period of years, it is less than the cost of replacing batteries in the old type.

Write for literature and prices—or order direct from

George P. Pilling and Son Company
3451 WALNUT STREET
Philadelphia

A Standing Invitation. When in Philadelphia, visit our modern sales rooms and manufacturing plant. Free parking on our private lot.

INSTRUMENTS BY— Pilling

PILLING FOR PERFECTION in surgical instruments

Bindings for Review Copies

THE AMERICAN REVIEW OF TUBERCULOSIS will bind current and back numbers of the REVIEW in standard uniform cloth binding.

Cost of binding, $3.00 per binding
Transportation and wrapping charges additional.

Please fill in the order below, detach this page and mail to:

AMERICAN REVIEW OF TUBERCULOSIS
1790 Broadway, New York 19, N. Y.

Please fill my order for binding my REVIEW volumes in the manner checked, supplying all the missing numbers.

☐ Original Articles and Abstracts of each volume separately at $6.00 per volume for binding.
☐ Articles and Abstracts for one volume in one binding at $3.00 per volume for binding.
☐ Articles and Abstracts for entire year bound separately at $3.00 per binding.

I desire volumes*..... bound and have sent to you at the above address under the date of.....by..... (Pp. or Express) Volumes.....

NAME.....

ADDRESS.....

*If you order Volumes XI and XII bound and wish them combined, check here ☐

1949 TRANSACTIONS

National Tuberculosis Association

Published as a record of the 45th Annual Meeting of the National Tuberculosis Association and its medical section, the American Trudeau Society. Contains papers by outstanding authorities presented before the clinical, surgical, sociological, nursing and laboratory research sections together with data describing the work of the Executive Office.

Approximately 500 pages
Price $3.00 *(foreign postage 25¢ extra)*

NATIONAL
TUBERCULOSIS ASSOCIATION
1790 Broadway
New York 19, New York

Industry, Tuberculosis Silicosis & Compensation

160 pages, clothbound, $2.00 postpaid

Edited by **Leroy U. Gardner, M.D.,** this useful volume assembles thirteen papers outlining significant developments in the handling of industrial X-ray surveys and follow-ups; in the identification and treatment of silicosis; in the field of workmen's compensation.

Recommended for thoughtful reading by industrial physicians, tuberculosis specialists, business and insurance executives.

Send your order today to the

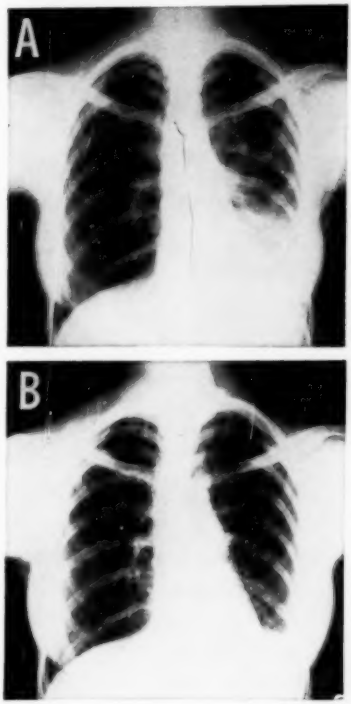
National Tuberculosis Association
1790 Broadway New York 19, N. Y.

Effective Chemotherapy in TUBERCULOSIS

Dihydrostreptomycin or Streptomycin, used alone or in combination with para-aminosalicylic acid, is recognized as a valuable and, in some instances, an essential adjuvant in the treatment of selected types and stages of tuberculosis.

Para-aminosalicylic acid is capable of inhibiting or significantly delaying the emergence of bacterial resistance to streptomycin or dihydrostreptomycin.

These drugs are not to be regarded as substitutes for traditional therapeutic methods. Rather, they serve best when properly integrated with bed rest and, where necessary, collapse measures or other forms of surgery.



A. Before Treatment
(9 days prior to Dihydrostreptomycin therapy) Diffuse lobular tuberculous pneumonia, lower half of left lung; thin-walled cavity above hilus (3 x 3.5 cm.).

B. After 3 Mos. Treatment
(2 days after discontinuance of Dihydrostreptomycin) Considerable clearing of acute exudative process in the diseased lung; cavity smaller and wall thinner.

Detailed literature on the subject of chemotherapy in tuberculosis will be supplied upon request.

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

Merck Antitubercular Agents

Streptomycin Calcium Chloride Complex Merck

Para-Aminosalicylic Acid Merck (PAS)

Dihydrostreptomycin Sulfate Merck

A WILL ROSS IDEA

One of a Number That Have Helped to Improve Service and Reduce Waste in Sanatoria

Along about 16 years ago Tuberculosis Sanatoria were faced with a special problem. Their patients used great quantities of sputum napkins. Keeping these patients supplied was a real problem because the piles of loose napkins quickly became soiled, they blew around or were pushed around and were wasted because patients would "grab" too many at a time. Altogether it was a pretty messy, wasteful business.

It was in 1934 that we developed the idea of Interfolded Sputum Napkins in a metal dispenser. An individual service, placed at each bedside, making it easy for the patient to quickly get one (two ply) clean napkin at a time, it proved a complete and satisfactory answer to the whole problem. It is now serving Tuberculosis Sanatoria all over the country.

This idea in itself may have little or no interest to hospitals in general except as an example of the type of service we have tried to render to all hospitals large or small, of whatever nature. Knowing our customers' problems and having "ideas" that help them find solutions is one reason why Will Ross, Inc., in less than 36 years, has grown from a little mail order house to a national institution.

WILL ROSS, INC.

Manufacturers and Distributors of Hospital and Sanatorium Supplies and Equipment

MILWAUKEE 10, WISCONSIN

THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 61 | *June 1950* | NUMBER 6

AN EVALUATION OF THE METHOD OF QUANTITATIVE AIRBORNE INFECTION AND ITS USE IN THE STUDY OF THE PATHOGENESIS OF TUBERCULOSIS[1,2]

MAX B. LURIE, A. G. HEPPLESTON,[3] SAMUEL ABRAMSON,[4] AND IRENE B. SWARTZ

(Received for publication January 13, 1950)

INTRODUCTION

It has been shown in a previous study (1) that rabbits of different genetic resistance to tuberculosis, exposed to a single quantitative inhalation of droplet nuclei of virulent, bovine-type tubercle bacilli, develop different types of tuberculosis. These types closely simulate the various patterns of the disease acquired by rabbits of similar genetic constitutions when naturally exposed to tuberculous roommates (2). It has also been demonstrated that localized, ulcerative phthisis can be produced in sensitized rabbits of high genetic resistance to the disease by an inhalation of small, known numbers of virulent bacilli (3). The disease thus induced is comparable both in its inception and its progression to chronic ulcerative pulmonary tuberculosis as commonly seen in man. This same method of quantitative airborne infection has been used to determine the efficiency of masks in protecting rabbits against the inhalation of airborne tubercle bacilli (4). The behavior of inhaled human-type bacilli in rabbits of unknown genetic resistance to tuberculosis has also been studied by the same procedure (5).

Wells has described an apparatus for quantitative, experimental airborne infection (6) and has discussed certain phases of the mechanics of the inception of airborne pulmonary disease (7). It is the purpose of the present report to analyze and evaluate this method of infection by the use of an apparatus based on the principles elaborated by Wells but so modified as to improve its quantitative efficiency and the ease and safety of its manipulation in elucidating certain aspects of the pathogenesis of tuberculosis.

In addition to defining the efficiency and predictability of this modified

[1] From The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pa.

[2] Aided by grants from the Commonwealth Fund, the National Tuberculosis Association, and the Federal Security Agency, Public Health Service.

[3] Dorothy Temple Cross Research Fellow, Medical Research Council of Great Britain.

[4] Division of Tuberculosis, Federal Security Agency, Public Health Service.

apparatus in infecting rabbits with human or bovine tubercle bacilli, this study gives information on the relationship of the number and size of the infectious particles of these organisms to the origin of pulmonary disease in the rabbit as well as on the nature of the resistance of this animal to both types of tubercle bacillus.

METHODS AND MATERIALS

The Modified Wells Apparatus for Quantitative Airborne Infection and its Use

The principles of the apparatus are given by Wells, but it is necessary to describe our modified apparatus in order to assess the performance of its in-

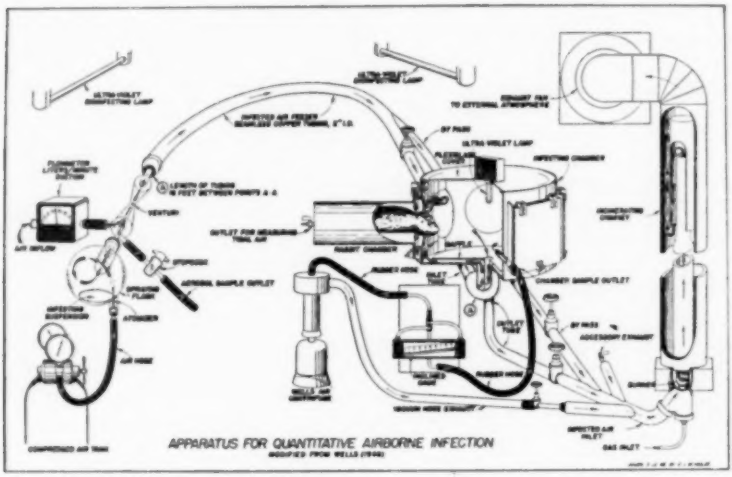


FIG. 1. The apparatus for quantitative airborne infection modified from Wells (1948).

novations. Figure 1 gives a schematic drawing of the entire apparatus as assembled for use.

Compressed air, at 20 pounds per square inch, is introduced into a specially designed Florence spraying flask (6) through a nozzle. The latter consists of an 18-gauge hypodermic needle, the bevel of which has been cut off, enclosed in a glass sleeve of 3 mm. internal diameter. Near the lower third of this sleeve there is an aperture of about 3 mm. in diameter. The sleeve extends about 17 mm. beyond the tip of the hypodermic needle. The whole nozzle, mounted firmly in a rubber stopper, fits tightly into an accessory neck placed tangentially to the circumference of the flask, the neck lying well below the level of the bacterial suspension. This supension is atomized into a fine mist by the air jet. The larger droplets return to the flask while the aerosol is carried into a mixing chamber via a T tube provided with a large stopcock on its vertical limb.

The mixing chamber consists of two Erlenmyer flasks of 250 and 500 ml. capacity fused at their necks. In the center of the base of the proximal and distal flasks, respectively, there is an entrance and an exit. The aerosol is delivered at the point of constriction of the two flasks by means of a tapering tube which is fused to the entrance hole. The air of the room

is sucked into the mixing chamber through a side arm fused into the side wall of the proximal flask near its base. The aerosol and the diluting-room air thus meet at the point of junction of the two flasks and are mixed in the distal flask.

From this mixing chamber the infected air is drawn into a copper pipe, 2 inches in diameter and 16 feet long. At a convenient point this duct bifurcates, one division leads into the exposure chamber and the other by-passes the latter and enters the incinerating chimney. Air-tight gate valves are introduced into the conduit to assure the desired flow of infected air into or past the exposure chamber.

The infected air enters the cylindrical exposure chamber at the bottom, where it is deflected to the periphery by means of a flat, circular baffle plate which extends to within 5 cm. of the wall of the chamber and about 2.5 cm. above its floor. The infected air is then drawn past the six portholes through which the rabbits' heads project into the chamber. Their bodies are contained within six cylinders radially attached to these portholes. The rabbits' heads are separated from the cylinders by means of adjustable collars which fit into movable platforms within the cylinders (figure 2). Suitable rubber gaskets are provided at the planes of contact between the cylinders and the chamber.

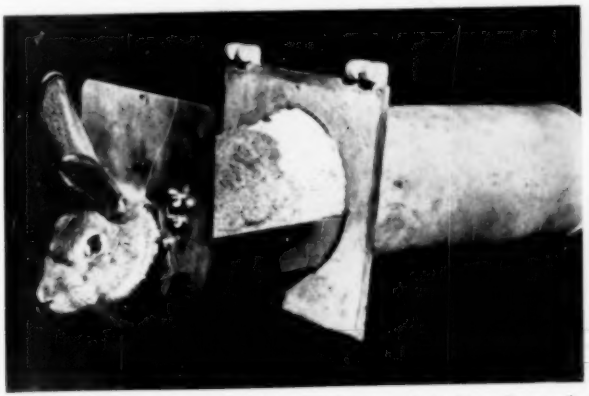


FIG. 2. The movable platform of the cylinder with its adjustable collar to fit the rabbit's neck.

The infected air is drawn out of the chamber through a central exit pipe and into an incinerating chimney as described by Wells (8). The air supporting the gas flame at the bottom of the chimney is derived solely from the infected air that leaves the system. The flame is generated by a large Fisher burner provided with a suitable device for its spread. As described by Wells, the incinerating chimney consists of three concentric "Transite" pipes with suitable baffles to ensure that the infected air first passes through the flame upward to the top of the central pipe, then downward through the middle pipe and finally upward and outward through the peripheral large pipe to the exit. This is provided with a powerful fan which discharges the incinerated, disinfected air to the outside atmosphere. All points in the system are airtight, except where the air of the room is drawn into the system. This is effected by the draught action of the incinerator flame and that of the exit fan, both of which provide a considerable negative pressure throughout the system. The room air enters the proximal portion of the mixing chamber at the rate of 80–90 liters per minute, judging by a flowmeter attached as shown in figure 1. This also indicates whether the system is under negative pressure and so guards the safety of all operations.

Preparation of the suspension for atomization: A young culture of tubercle bacilli of the human type, H37Rv, or of the bovine type, Ravenel, grown on a modified Lowenstein

medium (9) or on glycerol agar was ground in an agate mortar with the aid of a few drops of bile and suspended in fifteenth molar sodium acid phosphate to contain approximately 10 mg. per ml. This suspension was then treated in one of two ways. In the first method, the suspension was slowly centrifuged for about one minute and a 1:10 dilution of the supernatant fluid was filtered through one or two layers of Whatman No. 5 paper to remove the clumps. This yielded a suspension in which the majority of the microorganisms were present as isolated individuals but which still contained up to 5 per cent of clumps, consisting of as many as 20 or more microorganisms (figure 3). By the second method, the suspension containing approximately 10 mg. per ml. was centrifuged at about 2,000 revolutions per minute for five minutes. The supernatant of this rapidly centrifuged suspension was then filtered through a sterile sintered glass filter of medium porosity at a negative pressure of 2 to 3 pounds per square inch. This type of treatment yielded a suspension in which nearly all the microorganisms were present as isolated cells and only occasionally could groups of 3 to 6

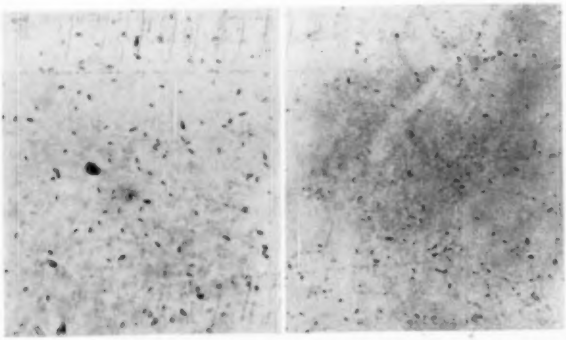


FIG. 3. (Left) A suspension of H37Rv centrifuged lightly and filtered through Whatman No. 5 filter paper; most of the bacilli are present as isolated cells; there are occasional clumps of microorganisms. Magnification × 1,000.

FIG. 4. (Right) A suspension of H37Rv, centrifuged for five minutes at 2,000 r.p.m. and filtered through sintered glass filter "M". All the bacilli are in the form of isolated cells. Magnification × 1,000.

bacteria be seen (figure 4). At no time were there larger clumps such as were found after filtration through Whatman No. 5 filter paper.

The opacity of each of the above suspensions was now determined in a Klett-Summerson photoelectric colorimeter and appropriate dilutions made in sterile fifteenth molar sodium acid phosphate prior to atomization. The flask was weighed before and after atomization and thus the amount of fluid delivered as aerosol per minute was ascertained. In some experiments the number of viable bacterial units per ml. of suspension before and after atomization was determined culturally.

To ensure the safety of the operators as well as to reduce the bacterial population of the room air which entered in the mixing chamber, four 30-watt germicidal ultraviolet lamps, emitting monochromatic rays of 2,537 Å were suitably placed in different parts of the room. A 4-watt, U shaped ultraviolet lamp was attached to the under surface of the transparent plexiglass cover of the exposure chamber. This plexiglass was specially treated to render it impervious to the ultraviolet light in the room.

The air sampling devices used: Both the Wells air centrifuge and the capillary impinger as modified by Rosebury (10) were used in these experiments. In both instances the exact amount of air sampled was determined by the same calibrated inclined draft gauge. The rate of air flow through these devices rarely exceeded 6 liters per minute. This air flow is

within the recommended range of the optimum performance of the devices used. The bacteria in the air sampled by both devices were trapped in glycerol broth. Dilutions of this broth were then cultured quantitatively on a modified Löwenstein's medium (9) and on Dorset's medium containing bone marrow infusion.

The aerosol: To induce a slowly progressive ulcerative tuberculosis with virulent bovine bacilli or to differentiate clearly the native resistance of various families of rabbits to this microorganism, it is imperative that the number of bacilli to which the rabbits are exposed be small. To meet this condition the number of bacilli in the air of the exposure chamber must often be reduced to such an extent that direct determination of their number per unit volume cannot be made. However, the number of bacilli per unit volume of aerosol as it leaves the spraying flask, before it is diluted by the room air, can always be determined. The dilution factor existing between the concentration of bacilli in this aerosol and that in the exposure chamber has been empirically determined in numerous experiments both with human and bovine tubercle bacilli. This factor depends in part on the volume of room air added to a unit volume of aerosol in a given time. The volume of air introduced as aerosol per unit time is given by the volume of compressed air used during a given period of atomization. Under the conditions of our experiments, about 8 to 12 liters of air per minute were introduced into the system to generate the aerosol. Since 80 to 90 liters of room air per minute were added to this aerosol through the side arm in the mixing chamber, one could anticipate that the concentration of the bacilli in the exposure chamber would be about one-tenth of that in the aerosol. If it is desired to expose rabbits to very small numbers of bacilli, sampling of the aerosol before exposing the rabbits to the infected air is made possible by the shunt through which the infected air by-passes the exposure chamber. The aerosol sample is drawn from the stopcock at the vertical limb of the T tube leaving the spraying flask.

Timing of exposure of rabbits: After the aerosol has been sampled, and with the infected air still by-passing the exposure chamber, the weighed rabbits are placed within the cylinders, their collars adjusted to fit each rabbit's neck as illustrated in figure 2, and the cylinders with their contained rabbits are securely attached to the portholes in the exposure chamber. The behavior of the rabbits within the chamber can be observed through the plexiglass cover. At a given moment the gate valves in the conduits are simultaneously operated by two workers in such a way that the infected air now enters the exposure chamber instead of the shunt. This is the commencement of the exposure of the rabbits. At least two samples of the infected air are taken from the exposure chamber during each experiment, one near the beginning and the other near the end of exposure. To terminate the exposure, the Wells spraying flask is turned on its axis in such a way that the bacterial suspension no longer enters the atomizer and only uninfected compressed air flows into the system. Simultaneously the ultraviolet lamp within the exposure chamber is turned on. By this combined maneuver the infected air is quickly drawn out of the chamber, the residual bacilli being killed almost instantaneously by the intense ultraviolet radiation.

The number of colonies cultured from the known volumes of chamber air

gives the concentration of bacillary particles per unit volume of air respired by the rabbits. The volume of infected air which the rabbits breathe is indicated by Kleiber's formula (11). This states that animals inhale 212 cc. of air per minute per Kg. of body weight to the three-quarter power in order to satisfy their oxygen requirements. In this way the number of bacillary particles respired by the rabbits is estimated.

After the termination of the exposure, the fresh air of the room is allowed to flush the exposure chamber in which the germicidal lamp continues to burn for at least half an hour. The rabbits are now safely removed from the exposure chamber. The air of the room, which is still irradiated with four 30-watt ultraviolet lamps, continues to flow through the entire system for an additional three to five hours after the termination of each experiment. During all this time the exposure chamber is irradiated by its own ultraviolet lamp. Before a new experiment is performed in the apparatus, the chamber is similarly cleansed for three additional hours.

EVALUATION OF THE PERFORMANCE OF THE APPARATUS AND ITS PREDICTABILITY

The aerosol: Our first concern is the number of viable bacillary particles present in a unit volume of aerosol. It will be recalled that the following data are directly observed: (a) the opacity of the original bacterial suspension; and (b) the dilution of the latter used for atomization; (c) the weight of this diluted suspension introduced into the system per minute; and (d) the volume of air in which the bacteria contained in this amount of fluid are suspended to form the aerosol. Since the bacterial suspension has a specific gravity of practically 1.0, it can be assumed that the weight of the suspension introduced per minute is equivalent to the volume of suspension converted into aerosol in the same time. Therefore, if the concentration of viable tubercle bacilli in a suspension of a certain opacity were known, and if all the particles atomized remained viable, then the number of bacterial particles present in a given volume of aerosol could be predicted, since a unit volume of air contained a known volume of this suspension. Unfortunately, however, the proportion of viable bacilli present in a given suspension of tubercle bacilli cannot be predicted from its opacity, owing to the effects of such factors as the particular strain of organism used, its age, the medium upon which it has been grown, and the degree of dispersion of the bacilli. Nevertheless, during the course of this work, in which numerous experiments were done both with human and bovine types of tubercle bacilli, it was assumed that a certain arbitrary number of viable bacilli are present in a suspension of tubercle bacilli of a given opacity. This arbitrary number was taken as 10,000,000 viable bacilli per ml. of suspension when its opacity was 100 in the Klett-Summerson colorimeter.

Human bacilli: Using bacterial suspensions of H37Rv, which were filtered through Whatman No. 5 paper, the number of bacilli per liter of aerosol actually cultured was, in the average of 8 experiments, not far different from the number of viable organisms calculated as present in the aerosol on the above assumption.

These results are shown in table 1. It will be seen that the median ratio be-

tween the estimated and observed number of bacilli in the aerosol is 0.9 or one-tenth more than was anticipated. Thus, in the experiment of June 24, 1948 the opacity of the filtered suspension was 28; therefore, taking the above arbitrary number as a standard, there were 2,800,000 viable organisms per ml. of suspension. The dilution used for atomization was 1:10. Hence, there were 280,000

TABLE 1

The Relation Between the Opacity of the Suspension of Human-type Bacilli to be Atomized, the Number of Bacterial Units Estimated as Contained in its Aerosol, and the Actual Number of Viable Units Cultured therefrom, when the Bacterial Suspension was Filtered through Whatman No. 5 Filter Paper

DATE OF EXPERIMENT	OPACITY OF ORIGINAL FILTERED SUSPENSION AND ITS ESTIMATED NUMBER OF BACILLI PER ML.	DILUTION OF SUSPENSION IN SPRAYING FLASK AND ITS ESTIMATED NUMBER OF BACILLI PER ML.	ML. OF SUSPENSION ATOMIZED PER MINUTE AND NUMBER OF BACILLI ESTIMATED AS INTRODUCED PER MINUTE	LITERS OF AIR INTRODUCED PER MINUTE WITH AEROSOL AND ITS ESTIMATED NUMBER OF BACILLI PER LITER	ACTUAL NUMBER OF BACILLI CULTURED PER LITER OF AEROSOL	RATIO BETWEEN ESTIMATED AND CULTURED NUMBER OF BACILLI IN AEROSOL
February 20, 1948, experiment A	7–700,000	1:7–100,000	0.25–25,000	10*–2,500	7,813	0.3
February 27, 1948, experiment A	5–500,000	1:10–50,000	0.23–11,500	12–958	3,714	0.3
February 16, 1948	11–1,100,000	1:10–110,000	0.21–23,100	11–2,100	4,545	0.5
January 30, 1948	9–900,000	1:10–90,000	0.23–20,700	10–2,070	3,524	0.6
February 20, 1948, experiment B	7–700,000	1:7–100,000	0.25–25,000	11–2,272	3,864	0.6
June 24, 1948	28–2,800,000	1:10–280,000	0.31–86,800	10–8,680	9,700	0.9
December 23, 1947	6–600,000	1:4.2–142,866	0.24–34,293	10*–3,429	2,629	1.3
February 27, 1948, experiment B	5–500,000	1:10–50,000	0.23–11,500	11–1,045	708	1.5
December 9, 1947	9–900,000	1:10–90,000	0.26–23,400	10–2,340	1,143	2.0
November 25, 1947	9–900,000	1:2–450,000	0.28–126,000	10*–12,600	4,266	3.0
March 23, 1948	20–2,000,000	Undiluted 2,000,000	0.24–480,000	12–40,000	9,821	4.1
					Average = 1.4 ±1.4	
					Median = 0.9	

* Volume of air introduced per minute assumed to be 10 liters.

microorganisms per ml. in the suspension to be atomized. Since 0.31 Gm. of suspension were atomized per minute, 86,800 viable bacteria were introduced into the system per minute. Since 10 liters of air per minute were introduced with the atomized suspension as aerosol, it follows that 8,680 bacilli per liter should have been recovered from the aerosol. Actually 9,700 were cultured. Hence the ratio between the estimated and the cultured was 0.9, which is a

good approximation. However, as will be noted in the remaining experiments, this ratio ranged from 0.3 to 4.1 with an average of 1.4. In other words, on the basis of the opacity of this type of suspension one could expect that the number of viable bacilli that could be isolated from the aerosol would be, on the average, in the neighborhood of 30 per cent less than the anticipated. It must be emphasized that this would be a very rough approximation, as the standard deviation was 100 per cent.

In table 1A are listed 8 experiments of the same type, except that the bacterial suspension used for atomization was filtered through sintered glass. It will be seen at once that the ratio between the expected and isolated bacilli in the

TABLE 1A

The Relation Between the Opacity of the Suspension of Human-type Bacilli to be Atomized, the Number of Bacterial Units Estimated as Contained in its Aerosol, and the Actual Number of Viable Units Cultured therefrom, when the Bacterial Suspension Was Filtered through Sintered Glass (M)

DATE OF EXPERIMENT	OPACITY OF ORIGINAL FILTERED SUSPENSION AND ITS ESTIMATED NUMBER OF BACILLI PER ML.	DILUTION OF SUSPENSION IN SPRAYING FLASK AND ITS ESTIMATED NUMBER OF BACILLI PER ML.	ML. OF SUSPENSION ATOMIZED PER MINUTE AND NUMBER OF BACILLI ESTIMATED AS INTRODUCED PER MINUTE	LITERS OF AIR INTRODUCED PER MINUTE WITH AEROSOL AND ITS ESTIMATED NUMBER OF BACILLI PER LITER	ACTUAL NUMBER OF BACILLI CULTURED PER LITER OF AEROSOL	RATIO BETWEEN ESTIMATED AND CULTURED NUMBER OF BACILLI IN AEROSOL
November 8, 1948	39–3,900,000	1:10–390,000	0.27–105,300	12–8,775	6,618	1.3
March 22, 1949	39–3,900,000	1:10–390,000	0.19–74,100	12–6,175	3,062	2.0
June 28, 1949	15–1,500,000	1:3–500,000	0.25–125,000	6–20,833	7,500	2.8
February 10, 1949	45–4,500,000	1:5–900,000	0.21–189,000	7–27,000	4,295	6.3
November 15, 1948	36–3,600,000	1:10–360,000	0.17–61,200	8–7,650	1,063	7.2
April 1, 1949	33–3,300,000	1:3–1,100,000	0.20–220,000	10–22,000	2,591	8.5
May 24, 1949	20–2,000,000	1:10–200,000	0.29–58,000	10*–5,800	522	11.1
May 18, 1949	25–2,500,000	1:6–416,666	0.23–95,833	11–8,712	614	14.2
					Average =	6.7
						±4.3
					Median =	6.8

* Volume of air introduced per minute assumed to be 10 liters.

aerosol in these experiments was five times greater than that in the previous experiments. The average ratio between the estimated and cultured bacilli in this group of experiments was 6.7 ± 4.3. Despite the great spread in the individual observations of both experiments, a statistical analysis of these two groups shows that the difference between them is highly significant, for the "P" value of the difference equals 0.002. The only known constant difference between these experiments is that Whatman filtered paper permits the passage of larger clumps than does the sintered glass. Therefore, it is probable that the explanation for the greater recovery of tubercle bacilli from the aerosol in the first instance may be attributed to the fact that larger particles are more completely removed from the air by the sampling methods used than the smaller particles.

Bovine bacilli: An essentially similar difference was found with bovine bacilli. As may be seen from table 2, where 21 experiments are listed, 8 of the 10 experiments with filtration through sintered glass showed that the expected number of bacilli per liter of aerosol was at least 2.5 times greater than the

TABLE 2

The Relation Between the Opacity of the Suspension of Bovine-type Bacilli to be Atomized, the Number of Bacterial Units Estimated as Contained in its Aerosol, and the Actual Number of Viable Bacilli Cultured therefrom

DATE OF EXPERIMENT	CAPACITY OF ORIGINAL FILTERED SUSPENSION AND ITS ESTIMATED NUMBER OF BACILLI PER ML.	DILUTION OF SUSPENSION IN SPRAYING FLASK AND ITS ESTIMATED NUMBER OF BACILLI PER ML.	ML. OF SUSPENSION ATOMIZED PER MINUTE AND NUMBER OF BACILLI ESTIMATED AS INTRODUCED PER MINUTE	LITERS OF AIR INTRODUCED PER MINUTE WITH AEROSOL AND ITS ESTIMATED NUMBER OF BACILLI PER LITER	ACTUAL NUMBER OF BACILLI CULTURED FROM AEROSOL PER LITER	RATIO BETWEEN ESTIMATED AND CULTURED NUMBER OF BACILLI IN AEROSOL
November 24, 1948-S	(S)22-2,200,000	1:3-733,333	0.30-220,000	15-14,666	22,000	0.7
April 8, 1948-R	30-3,000,000	1:5-600,000	0.25-150,000	12-12,500	13,194	0.9
January 22, 1948-R	27-2,700,000	1:10-270,000	0.27-72,900	11-6,627	6,429	1.0
November 13, 1947-R	16-1,600,000	1:5-320,000	0.27-86,400	11-7,850	5,000	1.6
May 26, 1948-S	(S)8-800,000	1:5-160,000	0.28-44,800	10*-4,480	2,500	1.8
December 16, 1947-S	11-1,100,000	1:15-73,300	0.23-16,859	10-1,686	827	2.0
March 8, 1948-S	27-2,700,000	1:10-270,000	0.24-64,800	11-5,891	2,619	2.2
April 20, 1948-R	30-3,000,000	1:10-300,000	0.24-72,000	10-7,200	3,193	2.3
March 10, 1948-R	57-5,700,000	1:10-570,000	0.20-114,000	9-12,666	5,192	2.4
May 4, 1948-S	13-1,300,000	1:5-260,000	0.24-62,400	12-5,200	2,190	2.4
May 6, 1949-S	(S)49-4,900,000	1:15-326,600	0.21-68,586	7-9,798	3,913	2.5
February 12, 1948-R	(S)8-800,000	1:3-266,600	0.22-58,652	10*-5,865	2,083	2.8
March 29, 1948-R	25-2,500,000	1:5-500,000	0.22-110,000	11-10,000	3,587	2.8
January 28, 1949-S	(S)17-1,700,000	1:10-170,000	0.18-30,600	8-3,825	1,296	3.0
February 10, 1948-S	(S)35-3,500,000	1:10-350,000	0.25-87,500	10-8,750	2,546	3.4
December 22, 1948-S	(S)32-3,200,000	1:10-320,000	0.24-76,800	12-6,400	1,688	3.8
January 20, 1948-R	(S)51-5,100,000	1:10-510,000	0.22-112,200	10-11,220	2,810	4.0
January 4, 1949-S	(S)50-5,000,000	1:15-333,333	0.21-70,000	16-4,375	868	5.0
October 30, 1947-R	10-1,000,000	1:5-200,000	0.24-48,000	10-4,800	832	5.7
January 7, 1948-R	31-3,100,000	1:15-206,600	0.20-41,320	11-3,756	444	8.5
December 16, 1948-S	(S)30-3,000,000	1:10-300,000	0.18-54,000	15-3,600	352	10.2
					Average = 3.3 ±2.3	
					Medium = 2.5	

R—Ravenel strain grown on glycerol agar.

S—Ravenel strain grown on modified Löwenstein's medium.

(S) Suspension filtered through sintered glass filter (M); the remaining suspensions were filtered through Whatman No. 5 filter paper.

* Volume of air introduced per minute assumed to be 10 liters.

number actually recovered, whereas in 8 of the 11 experiments with paper filtration the expected number was at most 2.4 times the recovered, on the basis of the above assumption. However, the difference between these two types of experiments is not statistically significant. What is important for the predicta-

bility of the apparatus is that, within the conditions of these experiments, the number of bacilli per liter expected was 3.3 ± 2.3 times greater than that actually recovered, on the basis of the opacity of the suspension used for atom-

TABLE 3

The Relation Between the Number of Viable, Human-type Tubercle Bacilli in the Air of the Exposure Chamber at the Beginning and at the End of the Experiment

EXPERIMENT NUMBER	DATE OF EXPERIMENT	NUMBER OF TUBERCLE BACILLI PER LITER IN CHAMBER SAMPLE I; SAMPLING DEVICE USED. W = WELLS, R = ROSEBURY	INTERVAL IN MINUTES BETWEEN SUCCESSIVE SAMPLING	NUMBER OF TUBERCLE BACILLI PER LITER IN CHAMBER SAMPLE II; SAMPLING DEVICE USED. W = WELLS R = ROSEBURY	PERCENTAGE OF BACILLI FOUND IN CHAMBER SAMPLE I THAT WAS ISOLATED FROM CHAMBER SAMPLE II
1	February 16, 1948	215; R	9	47; R	22
2	November 8, 1948	450; W	15	112; W	25
3	November 15, 1948	73; W	15	27; W	37
4	May 24, 1948	8; W	15	3; W	38
5	May 18, 1949 (S)	44; W	14	18; W	41
6	March 22, 1949 (S)	168; W	15	78; W	46
7	January 30, 1948	104; R	8	52; R	50
8	February 4, 1948	65; R	25	35; R	54
9	February 27, 1948, Experiment A	71; W	10	41; R	58
10	December 23, 1947	34; R	7	21; W	62
11	December 9, 1947	76; W	7	50; R	65
12	February 20, 1948, Experiment B	229; W	15	156; R	68
13	February 20, 1948, Experiment A	188; R	15	130; W	69
14	June 25, 1948	158; W	15	110; W	70
15	June 28, 1949 (S)*	231; W	15	202; W	87
16	November 25, 1947	230; W	9.5	209; W	91
17	April 1, 1949 (S)	15; W	15	18; W	120
18	February 27, 1948, Experiment B	10; R	12	14; W	140
19	June 24, 1948	111; W	15	180; W	162
				Average = 68	
				Median = 62	

(S) The bacterial suspensions in these experiments were filtered through sintered glass before atomization; in the remaining experiments the suspensions were filtered through Whatman No. 5 filter paper before atomization.

* The suspending medium for the bacilli atomized in this experiment consisted of one volume of M/15 Na_2HOP_4 and two volumes of 0.1 per cent of bovine albumin.

ization. It is noteworthy that in more than half of these experiments this factor ranged between 1.6 and 3. Hence the opacity of the suspension used for atomization of bovine bacilli gives a fairly good idea of the number of viable bacilli likely to be recovered from the aerosol. We have no explanation as to why the variation is less with bovine bacilli than with human.

The Concentration of Bacilli in the Exposure Chamber

While the concentration of viable bacillary particles in the aerosol is predictable to a certain degree from the opacity of the suspension used for atomization, it is more important to be able to predict the number of viable bacillary particles per unit volume of air in the exposure chamber which may be obtained from the

TABLE 4

The Relation Between the Number of Viable Bovine-type Tubercle Bacilli in the Air of the Exposure Chamber at the Beginning and at the End of the Experiment

DATE OF EXPERIMENT AND STRAIN OF RAVENEL USED	NUMBER OF TUBERCLE BACILLI PER LITER IN CHAMBER SAMPLE I; SAMPLING DEVICE USED. W = WELLS, R = ROSEBURY	INTERVAL IN MINUTES BETWEEN SUCCESSIVE SAMPLING	NUMBER OF TUBERCLE BACILLI PER LITER IN CHAMBER SAMPLE II; SAMPLING DEVICE USED. W = WELLS, R = ROSEBURY	PERCENTAGE OF BACILLI FOUND IN CHAMBER SAMPLE I THAT WAS ISOLATED FROM CHAMBER SAMPLE II
December 22, 1948; S, (S)	57; W	15	5; W	26
April 20, 1948; R	86; W	15	25; W	29
January 4, 1949; S, (S)	66; W	15	22; W	33
October 15, 1947; S	257; W	12.5	92; W	36
May 26, 1948; S, (S)	89; W	19	37; W	42
March 29, 1948; R	67; W	15	32; R	48
April 2, 1948; R	270; R	15	132; W	49
March 8, 1948; S	31; R	15	16; W	52
November 13, 1947; R	107; W	15	57; R	53
June 21, 1948; S	212; W	20	120; W	57
January 28, 1949; S, (S)	24; W	15	14; W	58
May 6, 1949; S, (S)	121; W	15	84; W	70
March 10, 1948; R	41; W	15	30; R	73
February 10, 1948; S	17; R	15	13; R	76
January 20, 1948; R	21; R	15	19; R	90
December 16, 1948; S, (S)	39; W	6	42; W	108
May 4, 1948; S	44; W	13	56; W	127
May 28, 1948; S	155; W	20	203; W	131
November 24, 1948; S, (S)	850; W	30	1,607; W	188
			Average = 71	
			Median = 57	

(S) Bacterial suspensions in these experiments were filtered through sintered glass before atomization; in the remaining experiments the suspensions were filtered through Whatman No. 5 filter paper.

S = Ravenel cultured on Löwenstein's medium.

R = Ravenel cultured on glycerol agar.

atomization of a given suspension. For this reason it is necessary to analyze the results obtained from the sampling of the air in the exposure chamber, and to determine whether there is a constant relationship between the concentration of the bacilli in the aerosol and that in the exposure chamber.

As was found in the first studies by this method (1), a sample of air taken from the chamber at the beginning of the exposure usually contained more viable

bacilli than a sample taken toward the end of the exposure. In the present investigation this was, in general, confirmed, irrespective of whether human or bovine tubercle bacilli were used. This is shown in tables 3 and 4. Thus in table 3, where human-type tubercle bacilli were used, in 14 of 19 experiments the second chamber sample contained from 22 to 70 per cent of the bacillary viable particles present in the first sample. In only 5 experiments was the recovery from the second sample greater. The average number of bacilli recovered from the second sample was 68 per cent of that of the first sample, with a median recovery of 62 per cent. Whether the sampling was done by the Wells air centrifuge or by the capillary impinger, the same tendency was observed.

TABLE 5

The Effect of Atomization of Suspensions of Tubercle Bacilli in M/15 Na_2HPO_4 on Their Content of Viable Organisms

TYPE OF TUBERCLE BACILLI USED	NUMBER OF VIABLE BACILLI PER ML. BEFORE ATOMIZATION	DURATION OF ATOMIZATION IN MINUTES	NUMBER OF VIABLE BACILLI PER ML. AFTER ATOMIZATION	PERCENTAGE SURVIVAL OF BACILLI AFTER ATOMIZATION
Ravenel	140,000	25	22,000	16
Ravenel	12,600	28	2,300	18
Ravenel	8,000	—	2,000	25
Ravenel	1,080,000	29	280,000	26
Ravenel	125,000	41	39,000	31
Ravenel	300,000	20	113,000	38
Ravenel	90,000	21	35,000	39
Ravenel	106,000	30	53,000	50
Ravenel	3,000	—	1,600	53
Ravenel	3,800	—	2,300	61
Ravenel	4,400,000	30	2,880,000	63
P 15 B	580,000	33	410,000	70
Ravenel	4,000	30	3,800	95
P 15 B	220,000	30	220,000	100
Ravenel	4,460,000	32	4,800,000	107
Ravenel	1,230,000	32	1,600,000	130
			Average = 57	
			Median = 52	

There was no clear evidence for the superiority of the Rosebury device over the Wells air centrifuge in the number of viable bacillary particles which could be obtained from a given chamber sample. This can be seen in experiments 9, 10, 11, and 12, where it was found that the second sample was 64 per cent of the first, irrespective of whether the sampling was done with the one or the other device. Essentially the same observations were made when bovine bacilli were used (table 4). Again the second sample contained an average of 71 per cent of the viable organisms present in the first sample. The time interval between the two samplings ranged from six to thirty minutes in both types of experiments and most frequently was 15 minutes. Again there is no evidence for the better performance of one sampling device as compared with the other.

Reduction of number of bacilli during exposure: The regularity with which the bacilli in the exposure chamber decrease with the duration of the exposure requires explanation. If the concentration of viable bacilli in the spraying flask remained unchanged, the number of living organisms in the exposure chamber should also remain the same, for a constant amount of bacillary suspension in a constant amount of air is being introduced into the system throughout the experiment. The simplest explanation for the reduction of viable bacilli in the second chamber sample would be that the number of viable bacilli in the suspension that is being atomized gradually diminishes with the duration of the spraying. This, indeed, has been found to be the case. Thus, in table 5 are listed the number of bacilli per ml. of suspension before and after atomization. It will be noted that in the majority of the 16 experiments the number of bacilli in the suspension had markedly diminished after atomization, and at the end of thirty minutes of spraying the suspension contained about 57 per cent of their original number. This is not far different from the relationship between the concentration

TABLE 6

The Weight in Grams of Na_2HPO_4 Recovered from a Unit Volume (20 ml.) of M/15 Na_2HPO_4 in Spraying Flask Before Atomization and at Succeeding Half-hour Intervals of Atomization

NONE	DURATION OF ATOMIZATION IN HOURS					
	0.5		1.0		1.5	
Weight	Weight	Per cent increase over original	Weight	Per cent increase over original	Weight	Per cent increase over original
0.2642	0.2731	3.4	0.2868	8.6	0.3019	14.3
0.1946	0.2044	5.0	0.2090	7.4	0.2179	12.0
0.1991	0.2013	1.1	0.2078	4.3	0.2184	9.7

of viable tubercle bacilli in the 38 experiments listed in tables 3 and 4, where the second chamber sample contained approximately 70 per cent of the viable particles present in the first. This emphasizes the necessity for taking at least two chamber samples in each experiment, one at the beginning and the other at the end of exposure.

As to the cause for the gradual diminution of the viable bacilli in the spraying flask, it was found that this could not be accounted for by a dilution of the suspension for, as one can see in table 6, the concentration of salt in the menstruum increases with time. Nor could this mortality be explained on the basis of penetration of the ultraviolet energy of the exposure room into the spraying flask, as the germicidal lamps used emit monochromatic rays of 2,537 Å, to which the pyrex glass of the flask is impervious. While no definite information is available in this regard, it may be assumed that some of the bacilli are disrupted by the mechanical agitation incidental to atomization, or that the liquid used for suspending the bacilli, fifteenth molar sodium acid phosphate, itself may be slowly lethal to the bacilli.

The Aerosol–Chamber Ratio

It has been shown above that the number of viable bacilli present in the aerosol derived from a suspension of a given opacity can be predicted to a considerable degree, especially when bovine bacilli are atomized. Thus, with the constants used, the number of viable bovine bacilli in the aerosol was about one-third of the expected on the basis of the opacity of the suspension. Since about 10 liters of aerosol per minute are diluted with approximately 90 liters of room air in the

TABLE 7

The Relation Between the Number of Viable Human-type Bacillary Units in the Aerosol Emitted from the Spraying Flask and Their Number in the Exposure Chamber

DATE OF EXPERIMENT	NUMBER OF UNITS PER LITER IN AEROSOL	AVERAGE NUMBER OF UNITS PER LITER IN CHAMBER	AEROSOL-CHAMBER RATIO
December 9, 1947	1,143	63	18
November 25, 1947	4,266	219	20
February 20, 1948, Experiment B	3,864	192	20
May 18, 1949*	614	31	20
February 4, 1948	1,071	50	21
November 15, 1948*	1,063	50	21
November 8, 1948	6,618	281	24
March 22, 1949*	3,062	123	25
June 28, 1949	7,500	216	35
February 16, 1948	4,545	131	35
June 25, 1948	4,821	134	36
January 30, 1948	3,524	78	45
February 20, 1948, Experiment A	7,813	159	49
February 27, 1948, Experiment B	708	12	59
February 27, 1948, Experiment A	3,714	56	66
June 24, 1948	9,700	145	67
December 23, 1947	2,629	27	97
May 24, 1948*	522	5	104
April 1, 1949*	2,591	16	162
		Average = 49 Median = 36	

* The suspensions used in these experiments were filtered through sintered glass; in all the remaining experiments the suspensions used for atomization were filtered through Whatman No. 5 filter paper.

same time, one would anticipate that the concentration of viable organisms in the exposure chamber would be one-tenth of that in the aerosol. Actually, as will be seen in table 7, where human bacilli were used, this ratio was much greater and varied over a wide range from 18 to 162. In more than one-half of the 19 trials made, this ranged from 18 to 35. The average dilution factor between the concentration of bacilli in the aerosol and that in the exposure chamber was 49, with a median of 36. In other words, the number of bacilli in the exposure chamber contained, on the average, five times fewer microorganisms per unit volume than could be expected on the basis of air dilution alone. It will be noted

that filtration of the suspension to be atomized through Whatman No. 5 filter paper or through sintered glass had no constant effect on this dilution factor. Essentially similar results were obtained with bovine tubercle bacilli. Twenty such experiments are listed in table 8. Again, the dilution factor between the aerosol and chamber sample varied over a wide range. In 10 of these, this fell between 20 and 70 with an over-all average of 61, and a median of 46; that

TABLE 8

The Relation Between the Number of Viable, Bovine-type Bacillary Units in the Aerosol Emitted From the Spraying Flask and their Number in the Exposure Chamber

DATE OF EXPERIMENT	TYPE OF BACILLI	NUMBER OF UNITS PER LITER IN AEROSOL	AVERAGE NUMBER OF UNITS PER LITER IN CHAMBER	AEROSOL-CHAMBER RATIO
May 28, 1948	Ravenel S	1,679	179	9
December 16, 1948*	Ravenel S	352	40	9
June 21, 1948	Ravenel S	2,077	166	13
November 24, 1948*	Ravenel S	22,200	1,228	18
January 4, 1949*	Ravenel S	868	44	20
October 30, 1947	Ravenel R	832	31	27
May 6, 1949*	Ravenel S	3,913	103	38
May 26, 1948*	Ravenel S	2,500	63	40
May 4, 1948	Ravenel S	2,190	50	44
October 15, 1947	Ravenel S	7,794	174	45
December 22, 1948*	Ravenel S	1,688	36	47
November 13, 1947	Ravenel R	5,000	82	61
April 2, 1948	Ravenel R	13,194	201	66
January 29, 1949*	Ravenel S	1,296	19	68
April 20, 1948	Ravenel R	3,913	55	71
March 29, 1948	Ravenel R	3,587	49	73
March 8, 1948	Ravenel S	2,619	23	114
January 20, 1948	Ravenel R	2,810	19	140
March 10, 1948	Ravenel R	5,192	35	148
February 10, 1948	Ravenel S	2,546	15	170
			Average = 61 Median = 46	

Ravenel S = Ravenel cultured on Löwenstein's medium.

Ravenel R = Ravenel cultured on glycerol agar.

* The suspensions used in these experiments were filtered through sintered glass; in all the remaining experiments the suspensions used for atomization were filtered through Whatman No. 5 filter paper.

is, the concentration of viable bacillary units in a given volume of air in the exposure chamber was on the average one-sixtieth of that of the aerosol or six times less than the expected dilution of 1 in 10 on the basis of air dilution alone. Again, the type of filtration used for the suspension to be atomized did not affect this ratio.

The cause for the five- or six-fold reduction in the number of viable bacillary units present in the exposure chamber has not been determined. It may be

assumed that this reflects the mortality of the bacilli in the system. No constant relation was found between the temperature and/or the humidity of the room where the apparatus is situated and this mortality. However, the exact temperature and relative humidity within the exposure chamber was not assayed in the experiments. It is not impossible that these factors (12) together with other variables may play a role in this relation.

Summary: Hence, in summary, one may say that, starting with a suspension of a given opacity of human-type tubercle bacilli, the number of viable units per volume of air in the exposure chamber was, on the average, one-seventh of the expected on the basis of mere dilution, when the bacillary suspension to be atomized contained some coarse particles (an average of 1.4 reduction in the aerosol and a further fivefold reduction in the exposure chamber, or 1.4×5 which is 7). When the suspension to be atomized contained smaller particles this reduction was greater, being as much as one thirty-third of the expected (an average of 6.7 reduction in the aerosol and further fivefold reduction in the exposure chamber, or 6.7×5 which is 33). Thus the size of the particles atomized affected the number of viable units cultured from the aerosol but did not affect the dilution factor existing between the aerosol and the chamber. The average ratio between the number of human bacilli recovered from the chamber and the number expected from the opacity of the suspension is, therefore, 1:20. With bovine-type bacilli the number of viable units isolated from the exposure chamber was, on the average, one-twentieth of the expected, on the basis of dilution alone of a suspension of a given opacity (an average of a 3.3 reduction in the aerosol and a further sixfold reduction in the exposure chamber, or 3.3×6 which is 20).

While these are very far from constant factors, they nevertheless serve as a crude gauge of the number of viable units which may be expected to be present in a unit volume of air of the exposure chamber when the opacity of the suspension to be atomized is known and when all the variables involved in the performance of the apparatus are controlled.

These results thus emphasize the necessity of determining the concentration of viable units present in the exposure chamber or, when this is impossible, their number in the aerosol if any significant notion is to be obtained of the number of viable bacilli to which a given group of animals is exposed.

The Duration of the Exposure

One of the most gratifying features of the apparatus is the precision with which the duration of the exposure of a group of animals can be controlled.

As stated above, the cylinders containing the rabbits are secured to the portholes of the exposure chamber while the infected air is by-passing this chamber through the shunt. The exposure is begun by operating the gate valves simultaneously at a given moment in such a way that the infected air enters the exposure chamber instead of the shunt. Since about 100 liters of infected air enter the exposure chamber per minute, it follows that all of the uninfected air is exchanged by the contaminated air within 39 seconds, for the volume of the

exposure chamber is 65 liters. It will be remembered that the exposure is terminated at a given moment by shutting off the spray and simultaneously turning on the germicidal lamp within the chamber. The precision of the exposure depends upon how quickly the bacilli in the exposure chamber are removed and/or killed. To determine this, five-minute air samples were taken from the exposure chamber while the infected air was flowing through it. The introduction of the aerosol was then discontinued and the ultraviolet light within the chamber was turned on simultaneously. Immediately thereafter another five-minute sample was taken from the chamber.

TABLE 9

The Efficiency of Clearing the Exposure Chamber from Contained Tubercle Bacilli by Stopping the Atomization and Simultaneous Irradiation of the Chamber

EXPERIMENT NUMBER	NUMBER OF UNITS OF TUBERCLE BACILLI PER LITER OF AIR IN THE CHAMBER DURING ATOMIZATION	NUMBER OF UNITS OF TUBERCLE BACILLI PER LITER OF AIR IN THE CHAMBER IMMEDIATELY AFTER CESSATION OF ATOMIZATION	PERCENTAGE REMOVAL OF BACILLI FROM CHAMBER
1	357	1.4	99.6
2	568	0.5	99.9
3	1,500	0.5	99.97
4	16	0	100.0
5*	3	0	100.0

* Colon bacilli.

TABLE 10

Presence of Pathogenic Tubercle Bacilli in the Chamber at Different Intervals Following its Use

EXPERIMENT NUMBER AND STRAIN USED	INTERVAL FOLLOWING USE OF CHAMBER IN DAYS	NUMBER OF GUINEA PIGS EXPOSED	DURATION OF EXPOSURE IN HOURS	ESTIMATED NUMBER OF LITERS OF AIR RESPIRED BY EACH GUINEA PIG	INTERVAL BETWEEN EXPOSURE OF GUINEA PIGS AND ATUOPSY IN DAYS	PRESENCE OF TUBERCULOSIS AT AUTOPSY
1—H37Rv	5	3	3.5	12.6	80	0
2—Ravenel	1	3	1.0	3.6	47	0
3—Ravenel	1	3	1.0	3.6	99	0
4—H37Rv	1	3	3.0	10.8	91	0
5—Ravenel	1	3	2.0	7.2	87	0
6—Ravenel	1	3	4.75	17.1	97	0

Table 9 shows how many viable bacilli remained in the chamber after such a maneuver. It is clear that almost instantaneously more than 99.8 per cent of the bacilli present in the chamber during the exposure had been removed from it by the uninfected air flushing through it or had been killed by the ultraviolet energy of the lamp within the chamber. Thus, the maximum error in the duration of exposure under the conditions of these experiments is less than forty seconds. Since most of the rabbits were exposed for an observed time of thirty minutes or 1,800 seconds, it follows that the exposure time is actually about 2 per cent less than the observed period.

Contamination of exposure chamber from previous experiments: To determine whether any living tubercle bacilli can be released into the exposure chamber from a previous experiment, 6 groups of guinea pigs were placed within the exposure chamber one or five days following the flooding of the apparatus with either human or bovine virulent bacilli. In each instance listed in table 10, the system had been flushed with the fresh irradiated air of the room and the exposure chamber was irradiated for three or five hours after its use. There were 3 guinea pigs in each group. These were exposed for one to four and three-quarter hours in the chamber and each inhaled about 3 to 17 liters of this air. The guinea pigs were killed from the forty-seventh to the ninety-ninth day after exposure. In none of these 18 animals was any tuberculosis detected at autopsy. It is clear, therefore, that the flushing of the system with more than 20,000 liters of fresh air effectively cleanses the entire system and that, if any tubercle bacilli adherent to the walls of the conduit or to the rest of the apparatus are released into the air of the exposure chamber, they are not pathogenic after the customary precautions. Hence, one can be certain that when animals are subjected to a given infected air they are not inhaling any pathogenic microorganisms remaining in the system from a previous experiment and subsequently liberated into the air flow.

The Relation between the Number of Inhaled Bacillary Particles and the Number Arrested in the Lungs

In determining the effect of a quantitative exposure to a given microorganism on the lungs, one of the crucial questions is how many of the inhaled organisms actually reach the lung substance. It was stated above that the amount of air estimated as inhaled is given by Kleiber's formula. When the duration of exposure and the concentration of viable bacilli in the respired air is known, one can calculate the number of bacilli that each animal should inhale. If it is assumed that all of the bacilli inhaled localize in the lungs, it would follow that there would be a close correspondence between the number of bacillary particles estimated as inhaled and the number recovered from a uniform suspension of the lungs of such rabbits killed immediately after exposure.

Twenty-three experiments were done to test this view. Two samples of the air respired by the rabbits during their exposure to the infected air were cultured. Within one to two hours after exposure the rabbits were killed by air embolism. Under sterile conditions, the lungs were removed, freed from their bronchi, and weighed. They were placed in chilled, adequately sealed, sterile Waring blendors with a known volume of sterile fifteenth molar sodium acid phosphate and ground for four minutes. Known volumes of the uniformly suspended lung tissue were then planted either directly or after treatment with sulfuric acid on the modified Löwenstein and Dorset media (9). The number of colonies which grew out of a given weight of thoroughly ground lung was counted. Knowing the entire weight of both lungs, it was a simple matter to determine how many bacillary particles were present in both lungs. In the last column of table 11 is listed the percentage of bacilli calculated as inhaled that were actually recovered from the lungs.

TABLE 11

Ratio Between the Number of Tubercle Bacilli Estimated as Inhaled and the Number Cultured from the Lungs Shortly after Exposure

DATE OF EXPERIMENT	STRAIN USED	RABBIT NUMBER	NUMBER OF BACILLI ESTIMATED AS INHALED	NUMBER OF BACILLI CULTURED DIRECTLY (DIR) OR AFTER TREATMENT (TR) FROM BOTH LUNGS	PERCENTAGE OF BACILLI ESTIMATED AS INHALED THAT WERE RECOVERED FROM LUNGS
March 8, 1948	Ravenel S*	M-29	213	33 (Tr)	16
March 8, 1948	Ravenel S	M-31	157	29 (Tr)	19
April 20, 1948	Ravenel R**	M-52	555	130 (Tr)	23
March 29, 1948	Ravenel R	M-37	553	146 (Tr)	26
March 29, 1948	Ravenel R	M-42	572	172 (Dir)	30
October 15, 1947	Ravenel S	A10 = 77	2,646	907 (Tr)	34
May 4, 1948	Ravenel S	M-56	564	222 (Tr)	39
November 13, 1947	Ravenel R	J	1,346	565 (Tr)	42
April 1, 1949§	H37Rv†	C7-47	192	81 (Tr)	44
April 2, 1948	Ravenel R	M-46	2,190	1,027 (Dir)	47
May 26, 1948§	Ravenel S	C-8	843	397 (Dir)	47
May 4, 1948	Ravenel S	A-7	594	287 (Tr)	48
January 22, 1948	Ravenel R	M-11	138	75 (Tr)	54
November 8, 1948	H37Rv	Ca4-9	3,597	3,045 (Dir)	85
January 7, 1948	Ravenel R	AD2-21	94	99 (Tr)	101
April 20, 1948	Ravenel R	M-54	518	530 (Tr)	102
December 27, 1947	H37Rv	III3-1	413	534 (Dir)	129
November 13, 1947	Ravenel R	I	1,425	1,898 (Dir)	133
February 10, 1948	Ravenel S	M-14	194	255 (Tr)	131
May 6, 1949§	Ravenel S	IIIR2-2	1,648	2,634 (Tr)	160
June 28, 1949§	H37Rv	A9 = 126	3,240	5,190 (Tr)	160
March 10, 1948	Ravenel R	FCl-6	442	720 (Dir)	163
February 10, 1948	Ravenel S	M-15	167	317 (Tr)	190
				Average = 79 ±54	
				Median = 48	

* Ravenel S—Bovine bacilli grown on a modified Löwenstein's medium.

** Ravenel R—Bovine bacilli grown on a glycerol agar.

† H37Rv—Human-type bacilli grown on a modified Löwenstein's medium.

§ The suspensions used in these experiments were filtered through sintered glass; in all the remaining experiments the suspensions used for atomization were filtered through Whatman No. 5 filter paper.

It is evident that there was great variation in the percentage recovery in the different experiments. This ranged from 16 to 190 per cent of the expected. The average number of bacilli recovered was 79 per cent of those estimated as inhaled. Examination of the table, where the data are listed in the order of increasing percentage recovery, will reveal that in one-third of the experiments from 16 to 42 per cent of the bacilli estimated as inhaled were recovered from the lungs; in another third from 44 to 102 per cent were cultured; and in the last third of the trials more were found in the lung than were calculated as inhaled. Thus, while the number of bacilli estimated as inhaled, based on the number present in the respired air, is far from portraying the actual number of bacillary units retained in the lungs of each rabbit exposed, the approximation is of the order often encountered in this kind of biological experiment, as the average recovery was 79 ± 54 per cent of the expected.

TABLE 12

The Number of Bacillary Units of H37Rv, Calculated as Inhaled, Required to Generate a Single Primary Pulmonary Focus, when the Suspension to be Atomized was Filtered through Whatman No. 6 Filter Paper

DATE OF EXPERIMENT	RABBIT NUMBER	NUMBER OF UNITS CALCULATED AS INHALED	NUMBER OF PRIMARY FOCI GENERATED IN THE LUNGS	NUMBER OF BACILLARY UNITS YIELDING ONE TUBERCLE
November 25, 1947	H3	1,754	4	438
December 9, 1947	H8	473	1	473
December 23, 1947	A8 = 59	545	2	272
	III2-9	422	1	422
March 23, 1948	H24	442	1	442
June 25, 1948	FC2-7	2,250	28	80
			Average =	354

The Relation between the Number of Inhaled Particles of Human- and Bovine-type Tubercle Bacilli and the Number of Primary Tubercles Generated in the Lungs

Since it has been shown in the preceding section that the number of bacilli calculated as inhaled, based on the number present in the respired air, approximates the number of bacilli which are retained in the lungs, it is important to determine how many bacillary units of human- and bovine-type bacilli are necessary to generate a single primary pulmonary focus. At the same time attention was directed to the concentration and the dispersion of the bacilli in the air to which the animals are exposed in order to induce in them a disease which simulates that seen in both man and rabbits when they acquire the infection naturally. It will be remembered that in both species (2) primary pulmonary tuberculosis usually originates as a single parenchymal lesion.

Therefore, large numbers of rabbits of unknown and known genetic resistance to the disease were exposed to the inhalation of various concentrations of human and bovine type of virulent bacilli in different degrees of dispersion. When the exposed animals had developed a clearly defined tuberculin reaction, which

usually occurred between the fourth and fifth weeks following exposure, the rabbits were killed by air embolism. At this time the primary pulmonary foci had had no opportunity to coalesce or retrogress and secondary hematogenous or bronchogenic spread in the lungs had not yet occurred even in rabbits which had inhaled virulent bovine tubercle bacilli. The lungs were distended by intratracheal injection of neutral 10 per cent formalin and were then submerged in this fixative. The number of primary tubercles present in both lungs was then carefully determined by excising each individual focus.

TABLE 13

The Number of Bacillary Units of H37Rv, Calculated as Inhaled, Required to Generate a Single, Primary Pulmonary Focus, when the Suspension to be Atomized was Filtered through Sintered Glass

DATE OF EXPERIMENT	RABBIT NUMBER	NUMBER OF UNITS CALCULATED AS INHALED	NUMBER OF PRIMARY FOCI GENERATED IN THE LUNGS	NUMBER OF BACILLARY UNITS YIELDING ONE TUBERCLE
May 24, 1948	C1	59	2	29
	C2	58	3	19
	C3	58	4	14
	C4	63	2	31
March 22, 1949	Ca4-23	1,476	43	34
	Ca4-25	1,230	93	13
	Ca4-26	1,353	65	21
May 18, 1949	A9 = 83	589	15	39
	A9 = 109	558	13	43
	A9 = 116	651	41	16
	AD 2-1	465	13	36
	AD 2-16	620	26	24
	AD 2-23	620	26	24
			Average = 26 ±9	

Table 12 gives the relation between the number of human-type bacillary particles calculated as inhaled and the number of primary pulmonary foci that had developed in the lungs of 6 rabbits when the suspension to be atomized had been filtered through Whatman No. 5 filter paper. It will be remembered that such a suspension contained a considerable proportion of larger bacillary particles. The rabbits used in this group of experiments were 3 market rabbits of unknown resistance to tuberculosis and designated by the letter H; one rabbit of known high resistance to the disease, III 2-9; one of very low resistance, FC 2-7; and one of intermediate resistance, A8=59. It will be noted that the market rabbits and the animals of known high resistance to infection required more than 400 bacillary particles to generate a single tubercle. The rabbit of intermediate resistance required 272, and the rabbit of lowest resistance required 80

particles. The average number for these rabbits of varying resistance to infection was 354.

Clumps versus isolated microorganisms: Since the suspension atomized contained about 5 per cent of small clumps, it was thought that the great dispro-

TABLE 14

The Number of Bacillary Units of Bovine Bacilli Calculated as Inhaled Required to Generate a Single Primary Pulmonary Focus when the Suspension to be Atomized was Filtered through a Whatman No. 5 Filter Paper

DATE OF EXPERIMENT	RABBIT NUMBER	NUMBER OF UNITS CALCULATED AS INHALED	NUMBER OF PRIMARY FOCI GENERATED IN THE LUNGS	NUMBER OF BACILLARY UNITS YIELDING ONE TUBERCLE
May 4, 1948 S	M53	623	54	12
	M59	710	136	5
March 10, 1948 R	M33	367	21	17
	M34	331	23	14
May 28, 1948 S	AD2-31	3,496	223	16
	AD3 = 5	3,795	219	17
	AD3 = 9	2,979	126	24
January 22, 1948 R	M4	102	3	34
	M8	138	6	23
December 16, 1947 S	A	610	29	21
	B	603	8	75
	F	699	20	35
	K	645	7	92
April 20, 1948 R	M49	706	15	47
	M51	630	60	10
March 8, 1948 S	M25	183	12	15
	M28	193	4	48
March 29, 1948 R	M41	629	7	90
April 2, 1948 R	M45	2,730	27	101
	M47	2,309	32	72
			Average = 38 ±30	
			Median = 23–24	

R = Ravenel grown on glycerol agar.
S = Ravenel grown on modified Löwenstein's medium.

portion between the number of bacilli calculated as inhaled and the number of tubercles generated could be understood if it were assumed that only clumps of human-type tubercle bacilli multiply in the lung, whereas the 95 per cent of isolated organisms that were retained in the lungs failed to multiply and hence

failed to generate tubercles. That this is not a correct assumption is shown in table 13.

TABLE 15

The Number of Bacillary Units of Ravenel S, Calculated as Inhaled, Required to Generate a Single Primary Pulmonary Focus, when the Suspension to be Atomized was Filtered through Sintered Glass

DATE OF EXPERIMENT	RABBIT NUMBER	NUMBER OF TUBERCLE BACILLI CALCULATED AS INHALED	NUMBER OF TUBERCLES GENERATED	NUMBER OF BACILLI YIELDING ONE TUBERCLE
May 26, 1948	C6	1,085	197	5.5
	C7	991	61	16.2*
	C9	1,055	204	5.1
	C10	1,119	481	2.3
	AD2-19	1,393	213	6.5
December 16, 1948	AD3 = 5A	378	185	2.0
	AD3 = 6	378	207	1.8
	AD3 = 12	420	324	1.3
	AD2 = 24	420	130	3.2
	AD2 = 25	464	258	1.8
	AD2 = 30	378	163	2.3
December 22, 1948	AD2 = 32	553	106	5.2
	AD2 = 35	531	206	2.5
	AD2 = 38	575	208	2.7
	AD2 = 42	456	202	2.2
January 4, 1949	AD2 = 17	688	129	5.3
	AD2-22	688	149	4.6
	AD2-36	602	172	3.5
	AD3 = 7	645	158	4.1
	AD3 = 10	645	425	1.5
	AD3 = 13	559	164	3.4
January 28, 1949	III3-2	306	93	3.3
	III3-16	288	121	2.4
	III3-23	270	95	2.8
	III3-34	234	83	2.8
	III3-35	216	54	4.0
	III3-36	261	113	2.3
			Average = 3.3 ±1.4	

* Since this observation is entirely out of range of the 26 other observations, it is deemed proper to exclude this observation from the average.

A group of market rabbits and two groups of rabbits of known intermediate genetic resistance to tuberculosis were calculated to have inhaled, in three different experiments, from about 50 to 1,500 bacillary particles of the same

strain, H37Rv, as used in the previous experiments. The suspension used for atomization in these experiments, however, had first undergone a rapid centrifugation and had subsequently been filtered through sintered glass. This type of treatment yielded a suspension in which nearly all of the bacilli were present as isolated cells, and only occasionally were minute groups of 3 to 6 organisms present. It will be noted that the inhalation of practically isolated human-type cells, far from reducing the number of tubercles generated by a given number of inhaled bacilli, actually increased it more than tenfold, as the number of inhaled bacilli required to generate a single tubercle was, on the average, 26 instead of 354 of the previous experiment. Furthermore, there was no single instance in which the suspension containing coarser particles was as effective as the finely dispersed suspension in generating pulmonary foci.

It must be concluded, therefore, that isolated human-type bacilli when trapped in the lung parenchyma of a rabbit are capable of multiplication and of inciting the formation of pulmonary tubercles. Furthermore, the greater number of tubercles generated in the lung by the inhalation of isolated bacilli than by the inhalation of larger bacillary particles may be explained by the observations of Hatch (13) and of Wells and his associates (7) who found that the larger the particle the less likely for it to be lodged in the terminal part of the respiratory passages, where tuberculosis originates.

Equally clear evidence for the role of the size of the particle in penetrating the lung is given in tables 14 and 15, where the same two methods of filtration of the bacillary suspension before atomization were practiced on virulent bovine-type tubercle bacilli. Thus in table 14 are listed the number of bacilli calculated as inhaled which are required to generate a single pulmonary tubercle when the suspension is filtered through Whatman No. 5 filter paper and hence contains a considerable proportion of larger particles. The rabbits were estimated to have inhaled from about 100 to 3,800 viable bacillary units. It will be noted that the number of these particles required to generate a single pulmonary focus ranged between 5 and 101 in the 20 rabbits exposed to the inhalation of virulent bovine bacilli. The average was 38 $\pm$ 30 and the median, 23 to 24 bacillary units.

By contrast, in the 26 rabbits listed in table 15 which were exposed to the inhalation of the same virulent bovine bacillus, but in much finer degree of dispersion, the average number of bacillary particles required to generate a single tubercle was 3.3 $\pm$ 1.4 and ranged from 1.3 to 6.5. The suspensions used for the atomization of the bacilli in these experiments were subjected to a rapid preliminary centrifugation and subsequent filtration through sintered glass. Thus the tuberculogenic capacity of isolated bovine bacilli was ten times greater than that of coarser bacillary particles. As with human-type bacilli, the smaller the particle of bovine bacilli inhaled, the greater its efficiency in penetrating the lungs to generate tubercle.

The relation between the number of bovine bacilli estimated as inhaled and the number of grossly visible pulmonary foci generated is highly uniform, considering the multiplicity of variables concerned in the formation of tubercle. It must be emphasized, however, that while, on the basis of these results, about

3 bacillary particles of very small dimension are necessary to cause a single tubercle, in any one experiment, the range may vary 300 or more per cent in the individual animals. Thus in the experiment of January 4, 1949, when a group of 6 rabbits of the same genetic resistance had inhaled the same infected air, the number of bacilli required to generate a single tubercle varied between 1.5 and 5.3 in the different rabbits.

SUMMARY AND DISCUSSION

An endeavor was made to define the limitations of the method of quantitative airborne infection in tuberculosis and to determine the predictability of its performance. It was tested for its suitability to induce a disease which will closely simulate the tuberculosis acquired by rabbits of varying genetic resistance when they are naturally exposed to air contaminated by tuberculous roommates. As a result, information was obtained which cast further light on the number and size of the infectious particles of human or bovine bacilli concerned with the genesis of primary pulmonary lesions in the rabbit, as well as on the nature of the resistance of this animal to these two microorganisms.

The apparatus used was that described by Wells but so modified as to increase its quantitative efficiency and the safety of its application in the study of the pathogenesis of tuberculosis or other respiratory disease. Briefly, known volumes of suspension of virulent human- or bovine-type tubercle bacilli, in various degrees of dispersion and of known opacity, were atomized by known volumes of compressed air and introduced as aerosol at a uniform rate into a flowing system under negative pressure. This aerosol was safely diluted by a known volume of irradiated room air in a given time and carried into an exposure chamber in which rabbits of known weight inhaled the infected air for a known interval of time. The outflowing air was incinerated and then carried to the outside by a fan. The infected air could by-pass the exposure chamber by means of a shunt furnished with appropriate valves.

The concentration of the bacilli in the aerosol and in the exposure chamber was determined by a Wells air centrifuge or a Rosebury impinger, provided with a calibrated inclined draft gauge to measure the exact volume of air sampled. This sampled air was trapped in a known volume of glycerol broth and cultured on Löwenstein's and Dorset's media.

In many experiments the number of bacillary units arrested in the lungs was determined by quantitative culture of the organ immediately after exposure and compared with the number of bacilli estimated as inhaled. This estimate was based on the number of bacilli per liter of the air respired by the rabbits, the duration of their exposure, and on Kleiber's formula, which gives the amount of air an animal must respire to satisfy its basic oxygen requirements. In other experiments the number of primary tubercles generated in the lungs of rabbits of known and unknown genetic resistance to tuberculosis was determined, and the number of bacilli required to generate a tubercle by the inhalation of human and bovine bacilli under different degrees of dispersion was estimated.

If one assumes that a suspension of known opacity contains a certain constant

concentration of viable bacillary units, and that this number varies directly with the opacity, then the number of viable units cultured from a given volume of aerosol is predictable within limits. Thus the ratio between the expected and the actual number of viable units of bovine tubercle bacilli cultured from the aerosol averaged 3.3. However, the degree of dispersion of the bacilli in the suspension atomized exercised a deciding influence on this relation. If the suspension atomized contained larger particles, the recovery from the aerosol was, in general, more complete and in closer agreement with the expected. This is not surprising as it is well known that the larger the particles in the aerosol the more completely are they removed from the air sampled.

Since a unit volume of aerosol, delivered into the system per unit time, is diluted by a known volume of room air drawn into the system in the same time, one would anticipate a constant ratio between the concentration of the bacilli in the aerosol and that in the exposure chamber. However, the dilution factor between the concentration of viable bacilli in the aerosol and that in the exposure chamber, instead of being constant at 10 on the basis of simple dilution, was actually much greater. Part of this loss can be accounted for by an approximate 40 per cent mortality of the bacilli in the suspension during the process of its atomization. As a result of this, the concentration of the bacilli in the exposure chamber was about 30 to 40 per cent less at the end of the exposure period than at its beginning. What the other factors are which reduce the number of viable bacillary particles in the exposure chamber has not been determined. It is possible that fifteenth molar sodium acid phosphate, the fluid used for suspending the bacilli, may be slowly lethal to the microorganisms.

Whatever the mechanism involved, it was found that for bovine bacilli the average number of organisms cultured from the exposure chamber was in the neighborhood of one-twentieth of that anticipated (tables 2 and 8). For human-type bacilli, in fine dispersion, the average number of bacilli recovered from the exposure chamber was in the neighborhood of one-thirtieth of that expected (tables 1A and 7). These ratios, however, are not constant and varied greatly. Therefore, in order to obtain an estimate of the intensity of the exposure, the concentration of viable organisms in the air respired by the animals must be determined in each experiment.

In further preliminary experiments it was found that the predictability of the concentration of viable bacilli in the exposure chamber can be greatly increased by suspending the bacilli for atomization in 0.1 per cent of bovine albumin, as suggested by Fenner (14). By this means the number of bacilli recovered from the exposure chamber has been in the neighborhood of 40 to 80 per cent of the expected instead of the 3 to 5 per cent average recovery when the bacteria were suspended in fifteenth molar sodium acid phosphate.

The duration of the exposure of the animals is precisely controlled. Due to the shunt introduced into the conduit, by means of which the infected air can by-pass the exposure chamber, the error in the duration of the exposure time is no greater than 2 per cent. The bacilli are almost instantaneously removed and/or killed in the exposure chamber after cessation of atomization by the double action of

flushing the chamber with fresh air and by the intense ultraviolet irradiation. No residual pathogenic bacilli from previous experiments could be detected in the apparatus by subsequent exposure of guinea pigs in the chamber.

If, therefore, the air-sampling procedures used are adequate, the number of viable bacillary particles to which a given group of animals is exposed can be stated with considerable accuracy. It is noteworthy that in a large number of experiments, 79 ± 54 per cent of the bacilli calculated as inhaled were actually recovered from the lung immediately after exposure. Thus, the number of bacilli estimated as inhaled approximates that lodged in the lungs.

Since the natural airborne disease, both in man and in rabbits, originates as a single primary focus, it is necessary to determine the number and degree of dispersion of bacilli which must be inhaled to generate a single pulmonary tubercle. By causing rabbits to inhale bacilli atomized from suspensions containing either a small proportion of clumps or almost entirely isolated microorganisms, it was found that with both human- and bovine-type bacilli the number of viable units required to generate a single pulmonary focus depends on the size of the particles. The smaller the particles the greater their tuberculogenic capacity. With both types, ten times as many bacilli in coarse suspension were required to generate a single tubercle as in fine dispersion. This is in agreement with the studies of Hatch (13) on the penetration of dust particles of varying magnitude into the lung parenchyma and with the more direct observations of Wells, Rateliffe, and Crumb (7) on the tuberculogenic capacity of droplet nuclei of tubercle bacilli of varying rates of sedimentation. The number of bacilli cultured from the lungs was not influenced by the particle size in the respired air, however, for when the lung is cultured, the larger air passages as well as the respiratory bronchioli and alveoli are included in the inoculum. In the larger passages the big particles may be arrested but tubercles are generated only in the respiratory divisions of the bronchial tree, where only the smallest particles can penetrate. These observations indicate that the inhalation of microscopic droplet nuclei of tubercle bacilli is much more infectious than the aspiration of visible droplets.

With the same degree of dispersion, the number of tubercles generated by the inhalation of a given number of human-type bacilli is far less than that generated by the same number of bovine-type bacilli. Furthermore, as indicated by a few observations in table 12, and as will be elaborated in a subsequent study, the number of tubercles generated by inhalation of a given number of human-type bacilli is inversely related to the genetic resistance of the rabbit exposed. It has been shown by Heppleston (5) and confirmed since that living tubercle bacilli are present in microscopically normal lung parenchyma of rabbits which have inhaled human-type bacilli. Therefore, these bacilli may be present in the lung without engendering disease. Why is it that some bacilli in the lung generate tubercles while others fail to do so? Is this due to variations in the virulence of the bacilli or to differences in the resistance of the macrophages which ingest them?

The relationship between the number of isolated virulent bovine-type bacilli

estimated as inhaled and the number of tubercles generated in the lung was highly uniform; this ratio was 3.3 ± 1.4 in 26 rabbits of either unknown or intermediate genetic resistance to the infection. It follows, therefore, that both the number of bacilli estimated as inhaled and the number of tubercles generated

FIG. 5. The organs of the genetically susceptible rabbit, FFCI-1, and of the genetically resistant rabbit, SR2-8, four months after the simultaneous inhalation of an estimated number of 30 isolated bovine tubercle bacilli of the Ravenel strain. Rabbit FFCI-1 died of massive caseous pneumonia with enlargement and caseation of the draining tracheobronchial lymph nodes, pleural tuberculosis, hematogenous tuberculosis of both kidneys, tuberculosis of the bone marrow and of the appendix. Rabbit SR2-8 was killed on the day rabbit FFCI-1 died. There were a few slowly progressive tubercles in both lungs; one of these, in middle of the left lung, near its mesial border, has undergone central liquefaction. The disease is strictly localized to the portal of entry in the lung; there is no lymphogenous or hematogenous dissemination.

closely approximate the actual numbers involved or their multiples; otherwise there could be no uniform relationship between them.

Based on the above observation, a group of 6 normal rabbits, 3 of high genetic resistance (Race III) and 3 of low resistance (FC), inhaled simultaneously an estimated dose of about 30 bovine bacilli. One susceptible rabbit died in 106 days, with massive caseous pneumonia; enlargement and caseation of the tracheobron-

chial nodes; and hematogenous dissemination in the kidneys, bone marrow, skin, and intestines. On the same day one of the resistant rabbits was killed. Scattered small caseous lesions were found in the lung, some of which had undergone liquefaction and cavity formation. There was no lymphogenous or hematogenous spread from the portal of entry in the lung. This is illustrated in figure 5. Essentially the same differences in the pattern of the disease were found in the remaining 2 rabbits of each group. The susceptible rabbits died 156 and 179 days,

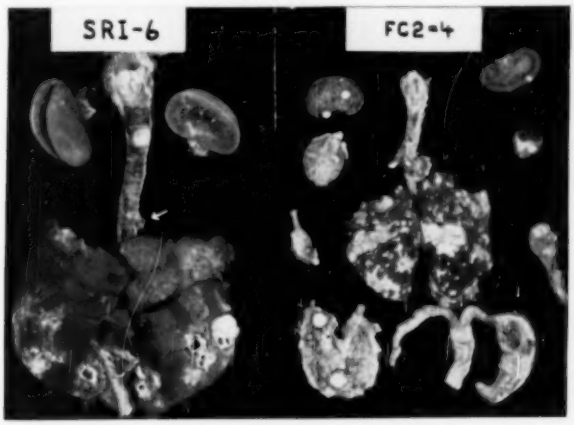


FIG. 6. The organs of the genetically susceptible rabbit, FC2 = 4, and of the genetically resistant rabbit, SRI-6, after the simultaneous inhalation of an estimated number of 30 isolated bovine tubercle bacilli of the Ravenel strain. Rabbit FC2 = 4 died 179 days after exposure with large caseous pneumonic lesions in both lungs and caseation of draining tracheobronchial lymph nodes. Diaphragmatic and pericardial tuberculosis are seen in the lower left corner and below the left kidneys, respectively. Hematogenous tuberculosis in the lungs, kidneys, and ileocecal junction, the latter between the heart and the diaphragm, is evident. Tuberculosis of the sclera of the left eye is depicted on the right. Below it may be seen the disease in the head of the left femur and of the bone marrow. Tuberculosis in the intrauterine inspissated fetus is depicted in the lower right corner. Rabbit SRI-6 died of asphyxia from tuberculous laryngitis 212 days after infection. Every lesion in the lung is excavated and encapsulated. There is no lymphogenous or hematogenous dissemination. The normal tracheobronchial lymph nodes are indicated by the arrow.

respectively, after exposure, with the same type of generalized disease as the first of their group. One of the two remaining resistant rabbits died of asphyxia from tuberculous laryngitis 212 days after infection, with localized ulcerative pulmonary phthisis of the reinfection type (figure 6). The third died of snuffles bronchopneumonia with localized ulcerative pulmonary phthisis, 278 days after exposure. It has thus been shown that the method of quantitative airborne infection as described in this study yields a disease which closely simulates the various forms acquired by resistant and susceptible animals when exposed to air contaminated by tuberculous roommates.

CONCLUSIONS

1. The population of viable bacilli in the suspension used to produce the aerosol for the quantitative exposure of animals declined during its atomization.

2. The number of viable bacillary units isolated from a given volume of aerosol, derived in turn from a unit volume of suspension of known opacity, was greater when the suspension contained some minute clumps than if nearly all of the bacilli were isolated.

3. With bovine- and human-type tubercle bacilli the concentration of viable bacillary units in the aerosol was, respectively, about one-third to one-fourth of that expected on the basis of the concentration of living organisms in a suspension of known opacity.

4. The concentration of viable particles in the exposure chamber was about five to six times less than the expected for human- and bovine-type bacilli, respectively, on the basis of dilution alone.

5. The predictability of the concentration of viable bacilli in the air of the exposure chamber, from the volume and opacity of the suspension atomized and its dilution, was only approximate and served merely as a guide in the computation of the desired intensity of exposure. Recent modifications in procedure promise greater accuracy in this respect.

6. Only direct measurement of the viable population of the air respired by the exposed animals can yield an adequate estimate of the number of living particles which they inhale.

7. The precision of timing of the exposure to quantitative airborne infection was accurate to within 2 per cent.

8. No viable pathogenic organisms could be shown to have remained in the exposure chamber from previous experiments.

9. The number of bacilli inhaled by exposed animals in a given time, as estimated on the basis of their oxygen requirements, is a rough approximation of the number of bacillary units which may be cultured from their lungs immediately after exposure.

10. The number of dispersed, human-type tubercle bacilli which must be inhaled by rabbits of intermediate resistance to the infection in order to generate a single visible primary pulmonary focus was about ten times greater than in the case of similarly dispersed bovine bacilli.

11. In confirmation of Wells and his associates: Irrespective of the type of bacilli inhaled, aerosols derived from bacillary suspensions which contain isolated tubercle bacilli were about ten times more tuberculogenic than aerosols derived from suspensions which contained larger bacillary groups.

12. The inhalation of about 3 viable, virulent bovine bacillary units in fine dispersion was required to generate a single primary pulmonary focus in rabbits of intermediate genetic resistance to the disease. The constancy of this relationship lends considerable credence to the estimate of the number of living particles arrested in the lung parenchyma.

13. This method of quantitative airborne infection is suitable for the induction

of a disease similar in character to that acquired by rabbits of varying genetic resistance when they are naturally exposed to air contaminated by tuberculous roommates.

14. The great disproportion between the number of dispersed human-type bacilli inhaled and the number of tubercles generated in the rabbit suggests that host factors suppress the growth of most of these bacilli in the lung. Conversely, the closeness between the number of dispersed bovine tubercle bacilli inhaled and the number of tubercles formed suggests that most bovine bacilli that lodge in the rabbit's lung grow and overcome the resistance of the host.

CONCLUSIONES

Valuación del Método Cuantitativo de Infección Aerógena y de su Empleo en el Estudio de la Patogenia de la Tuberculosis

1. La población de bacilos viables en la suspensión utilizada para producir el aerosol destinado a la exposición cuantitativa de los animales disminuyó durante la atomización del mismo.

2. El número de unidades bacilares viables aisladas de un volumen dado de aerosol, derivado a su vez de un volumen unitario de suspensión de opacidad conocida, fué mayor cuando la suspensión contenía algunos grumos minúsculos que cuando casi todos los bacilos eran aislados.

3. Con los bacilos tuberculosos de tipos bovino y humano, la concentración de unidades bacilares viables en el aerosol alcanzó, respectivamente, más o menos de la tercera a la cuarta parte de la esperada a base de la concentración de microbios vivos en una suspensión de opacidad conocida.

4. La concentración de partículas viables en la cámara de exposición fué aproximadamente de cinco a seis veces menor que la esperada, a base exclusiva de dilución, para los bacilos humanos y bovinos, respectivamente.

5. La predictibilidad de la concentración de bacilos viables en el aire de la cámara de exposición, por el volumen y la opacidad de la suspensión atomizada y de la dilución de la misma, fué muy aproximada y sirvió puramente como guía para la computación de la intensidad de la exposición deseada. Recientes modificaciones del procedimiento prometen mayor exactitud en este sentido.

6. Sólo la medición directa de la población viable del aire respirado por los animales expuestos puede suministrar un cálculo adecuado del número de partículas vivas que inhalan.

7. El cálculo del tiempo de exposición a la infección aerógena cuantitativa no se apartó en más de 2 por ciento de la precisión.

8. No pudo demostrarse que restaran, de los experimentos anteriores, microbios patógenos viables en la cámara de exposición.

9. El número de bacilos inhalados por los animales expuestos en un plazo dado, calculado a base de sus requisitos de oxígeno, constituye una aproximación tosca al número de unidades bacilares que puede cultivarse de los pulmones de aquellos inmediatamente después de la exposición.

10. El número de bacilos tuberculosos dispersos de tipo humano que tienen que inhalar conejos dotados de resistencia intermedia a la infección a fin de

generar un solo foco pulmonar primario visible fué aproximadamente diez veces mayor que tratándose de bacilos bovinos dispersados en forma semejante.

11. Confirmando la observación de Wells y colaboradores, independientemente del tipo de bacilos inhalados, los aerosoles derivados de suspensiones bacilares que contienen bacilos tuberculosos aislados fueron diez veces más tuberculógenos que los derivados de suspensiones que contenían grupos bacilares más grandes.

12. Para generar un solo foco pulmonar primario en conejos dotados de resistencia genética intermedia a la tuberculosis fué necesaria la inhalación de unas 3 unidades bacilares bovinas viables, virulentas, en fina dispersión. La constancia de esta relación presta considerable apoyo al cálculo del número de partículas vivas detenidas en el parénquima pulmonar.

13. Este método cuantitativo de infección aerógena se presta para la inducción de una enfermedad, semejante en su naturaleza a la adquirida por los conejos de variable resistencia genética, cuando se hallan expuestos en la naturaleza a aire contaminado por compañeros tuberculosos.

14. La gran desproporción entre el número de bacilos dispersos de tipo humano inhalados y el de tubérculos generados en el conejo indica que los factores presentes en el huésped suprimen el desarrollo de la mayor parte de dichos bacilos en el pulmón. A la inversa, la aproximación entre el número de bacilos tuberculosos bovinos dispersos inhalados y el número de tubérculos formados indica que la mayor parte de los bacilos bovinos que se alojan en el pulmón del conejo se desarrollan y vencen la resistencia del huésped.

Acknowledgment

We gladly acknowledge the able participation of Dr. Yin Chen Lee during the execution of some of this work.

REFERENCES

(1) Wells, W. F., and Lurie, M. B.: Experimental airborne disease: Quantitative natural respiratory contagion of tuberculosis, Am. J. Hyg., 1941, *34*, Sec. B, 21.

(2) Lurie, M. B.: Heredity, constitution and tuberculosis: An experimental study, Am. Rev. Tuberc., 1941, Supplement to vol. *44*, 1.

(3) Lurie, M. B., and Abramson, S.: Reproduction of human ulcerative pulmonary tuberculosis in rabbits by quantitative natural airborne contagion, Proc. Soc. Exper. Biol. & Med., 1948, *69*, 531.

(4) Lurie, M. B., and Abramson, S.: The efficiency of gauze masks in the protection of rabbits against the inhalation of droplet nuclei of tubercle bacilli, Am. Rev. Tuberc., 1949, *59*, 1.

(5) Heppleston, A. G.: Quantitative airborne tuberculosis in the rabbit: The course of human-type infection, J. Exper. Med., 1949, *89*, 597.

(6) Wells, W. F.: On the mechanics of droplet nuclei infection: I. Apparatus for the quantitative study of droplet nuclei infection of animals, Am. J. Hyg., 1948, *47*, 1.

(7) Wells, W. F., Ratcliffe, H. L., and Crumb, C.: On the mechanics of droplet nuclei infection: II. Quantitative experimental airborne tuberculosis in rabbits, Am. J. Hyg., 1948, *47*, 11.

(8) Wells, W. F.: An apparatus for the study of experimental airborne disease, Science, 1940, *91*, 172.

(9) LURIE, M. B.: The fate of BCG and associated changes in the organs of rabbits, J. Exper. Med., 1934, *60*, 163.

(10) ROSEBURY, T.: Experimental Airborne Disease, Baltimore, The Williams & Wilkins Company, 1947, p. 108.

(11) KLEIBER, M.: The tidal air of laboratory animals, Science, 1944, *99*, 542.

(12) PUCK, T. T., ROBERTSON, O. H., AND LEMON, H. M.: The bactericidal action of propylene glycol vapor on microorganisms suspended in the air: The influence of various factors on the activity of the vapor, J. Exper. Med., 1943, *78*, 387;

LOOSLI, C. G., LEMON, H. M., ROBERTSON, O. H., AND APPEL, E. L.: Experimental airborne influenza infection: Influence of humidity on survival of virus in air, Proc. Soc. Exper. Biol. & Med., 1943, *53*, 205;

DUNKLIN, E., AND PUCK, T. T.: The lethal effect of relative humidity on airborne bacteria, J. Exper. Med., 1948, *87*, 87.

(13) HATCH, T. A.: Behaviour of microscopic particles in the air and in the respiratory system in aerobiology (F. R. Moulton, editor), The American Association for the Advancement of Science, 1942, *17*, 102.

(14) FENNER, F., MARTIN, S. P., AND PIERCE, C. H.: Enumeration of viable tubercle bacilli in cultures and infected tissues, Ann. New York Acad. Sc., 1950, in press.

EXTRACTION OF PROTEINS AND OTHER CONSTITUENTS FROM THE TUBERCLE BACILLUS, WITH SOME OBSERVATIONS ON THEIR CHEMICAL AND BIOLOGICAL PROPERTIES[1, 2, 3]

ROBERT J. HECKLY AND DENNIS W. WATSON[4]

(Received for publication January 9, 1950)

INTRODUCTION

In a recent publication, Seibert (1) has described the isolation and characterization of three different proteins and two polysaccharides from unheated tuberculin. By using the unheated filtrates she was able to obtain proteins in a more native state than was possible when heated culture filtrates served as the source material. It is believed that the native proteins may yield more specific tuberculins because denaturation of proteins usually leads to decreased biologic specificity. Seibert (2) has stated also that the more denatured proteins elicit a lesser tuberculin skin reaction. Therefore, an attempt has been made to devise a method for extracting the proteins from young organisms with the least possible denaturation, rather than to depend on the action of autolytic processes to liberate the proteins. Procedures for rupturing and extracting tubercle bacilli have been described previously, but methods such as those used by Heidelberger and Menzel (3) or Chargaff and Saidel (4) involve the use of organic solvents to an extent which may not be advisable.

MATERIALS AND METHODS

Culture and media: A human strain of *M. tuberculosis*, TB-1[5], was employed for all of the work reported in this paper. The medium and technique used for mass cultivation of the organisms is that described by Dubos and Middlebrook (5).

The culture, growing as a pellicle, is allowed to incubate undisturbed for about 10 to 15 days at 37° to 38°C.

Harvesting of the cells: The entire contents of the culture bottles are emptied into a Büchner funnel lined with a single layer of gauze. No suction is applied. The collected mass of organisms is then washed two or three times with saline and allowed to drain free of ex-

---

[1] From the Departments of Chemistry and Agricultural Bacteriology, University of Wisconsin, Madison, Wisconsin.

[2] This study was made possible through a grant from the Committee on Medical Research and Therapy of the American Trudeau Society, medical section of the National Tuberculosis Association.

[3] Published with the permission of the Director of the Wisconsin Agriculture Experiment Station.

[4] Present address: Department of Immunology and Bacteriology Medical School, University of Minnesota, Minneapolis.

[5] TB-1 is the number of the stock culture of the Department of Agricultural Bacteriology, University of Wisconsin, Madison, Wisconsin. The culture originally came from the Bureau of Animal Industry.

cess liquid. The paste is then transferred to special heavy wall 100 ml. centrifuge tubes[6] containing glass beads or beads and sand. Approximately 20 Gm. of moist cells and 40 Gm. of beads were used per tube. The tubes are closed with good rubber stoppers, covered with gauze sponges saturated with disinfectant, and tied down with string.

Disintegration of the cells: The shaking technique was chosen for the disintegration of the tubercle bacilli because it appeared to be safe, convenient, and likely to yield a satisfactory product. The machine was modeled after one which had been constructed of wood and used by Anderson (6) to liberate enzymes from *Lactobacillus casei*. Similar methods have been used by others previously (7, 8). The holder for the glass tubes was built of sheet copper and so designed that it would not permit the escape of any organisms, should one of the glass containers break during the shaking operation. The tubes were maintained near 0°C. by proper adjustment of the amount of dry ice placed in the compartments on either side of the container.

The tubes containing the beads and organisms were shaken for 15 to 20 minutes at about 500 strokes per minute; the amplitude of each stroke was four inches. The shaking was not straight up and down, but rather the container described an arc with an 18- to 20-inch radius.

Extraction of the cells: After shaking, the entire contents of each tube was transferred to 250 ml. centrifuge tubes, the volume was brought to 150 ml. with saline-phosphate buffer,[7] and cooled to 0°C. After adding 50 ml. of ether at −70°C., the tubes were stoppered and thoroughly shaken by hand to form a stable emulsion. They were then frozen rapidly in dry ice with alcohol, and allowed to remain frozen for 12 to 24 hours. The mixture in the tubes was thawed, centrifuged at 1,000 r.p.m. for about 5 minutes, the aqueous phase removed by aspiration, and more buffer and ether added as before to re-extract the debris. The temperature was maintained between 0.5°C. and −0.5°C. during the entire ether treatment. A total of three extractions removed practically all of the water-soluble material. The extracts were pooled and sterilized by successive filtrations through a number 10, 02, and finally through a number 03 Selas filter. The ether and electrolytes were removed by dialysis against cold distilled water. All preparations were dried by lyophilization.

Electrophoresis: The Tiselius (9) apparatus, used in conjunction with the recent directions by Alberty (10), was employed to determine the composition of the various preparations. The concentration of the material at the time of examination varied because of technical difficulties imposed by the high velocity of some samples.

Fractionation procedure: Alcohol fractionation of the crude extracts was found to be impractical because of the high viscosity and interference by the nucleic acid. Therefore, an adsorption procedure was employed to effect at least a preliminary purification. The method chosen was one which had been employed previously in a study of *Bacillus anthracis* (11).

A typical adsorption procedure with calcium phosphate, as applied to the fractionation of the crude extract of the tubercle bacillus, is as follows. The crude extract is dissolved in 0.1 M phosphate buffer, pH 7.0, to yield about 0.1 to 0.5 per cent solution. While stirring vigorously, 10 ml. of 0.1 M calcium chloride are added slowly to 100 ml. of solution. It is then allowed to stand at room temperature for one to two hours before removing the precipitate by centrifugation. The supernatant is treated twice more with calcium chloride. It was observed that the pH drops gradually as the calcium chloride is added, and thus the final precipitate is removed at pH 6.5. The pooled precipitates are then washed twice with small volumes of 0.1 M phosphate buffer, pH 7.0, and finally dissolved in 0.5 M citrate buffer, pH 6.0 to 6.5. Both the supernatant solution and adsorbed material are then dialyzed against cold distilled water, and lyophilized.

---

[6] 100 ml. extra heavy Pyrex glass tubes, narrow neck, round bottom, No. 530, and rubber sleeve cushion, No. 670. International Equipment Co., 352 Western Avenue, Boston, Massachusetts.

[7] The buffer is a mixture of equal volumes of 0.85 per cent NaCl and 0.1 M phosphate buffer at pH 7.3.

Biologic testing: Guinea pigs were sensitized by subcutaneous inoculation in the groin with 0.1 ml. of a suspension of *M. tuberculosis*, strain DT, prepared by washing the growth from the solid egg yolk medium. For testing, both the standard PPD and the unknown preparations were dissolved at 1.0 to 10 mg. per ml. in a sterile phosphate buffer[3] recommended by Seibert (12). The stock solutions thus obtained were dispensed, 0.5 ml. per vial, frozen in dry ice, and kept in a deep freezer until ready for use. The buffer used for diluting the samples for testing has the same composition as the one indicated above, except that 8.0 Gm. NaCl are added per liter and the phenol is omitted. The pH after sterilization was 7.3. Known amounts of a standard PPD preparation were injected intracutaneously into the left flank of a guinea pig, and the unknown was injected into the right flank of the same animal, in 0.1 ml. of solution. The two axes of the ellipsoidal reaction were measured at 24 and 48 hours, and the thickness of the lesion was estimated on a scale of 1 to 4. Only the 48-hour observations are recorded in the tables presented here.

Chemical analytical methods: Desoxyribonucleic acid was determined by the use of the Dische's (13) diphenylamine reagent as described by Kabat and Mayer (14). Carbohydrate was estimated by use of the anthrone reagent described by Morris (15), using a purified tuberculin polysaccharide as a primary standard. The samples for the nitrogen determinations were digested with sulfuric acid and copper selenite catalyst. The determinations were made by micro-Kjeldahl or Nesslerization procedures.

TABLE 1

A Comparison of the Amount of Material Rendered Extractable from M. tuberculosis by Treatment with Various Abrasives

ABRASIVE AGENT	WET WEIGHT OF CELLS	MG. OF N PER GM. OF CELLS*
	gm.	
No. 12 glass beads	22.5	0.53
Sand and 4 mm. glass beads	31.5	0.74
4 mm. glass beads	27.5	0.55
Sand only	20.0	0.55
Sand and 4 mm. glass beads	34.0	0.54

* Total nitrogen extracted calculated from micro-Kjeldahl determinations of aliquots.

RESULTS

Abrasives: In the shaking procedure, which ruptures the cells and yields a crude water-soluble extract, various abrasives have been used. As shown in table 1, there is little difference between those tested. Although others (7, 8) have reported that the smaller beads produce the best breaking or killing of cells, a limited number of experiments with *M. tuberculosis* did not confirm their results. The results of an experiment to determine the effect of varying the type of abrasive are given in table 1. The ratio of mg. nitrogen extracted per gram of bacilli, wet weight, is employed as an index of the amount of material rendered water soluble. The differences between the various tubes were not great, but it seems that sand and 4 mm. glass beads may be the most efficient. Other less quantitative experiments, in which only the weights of the final

[3] 4.774 Gm. $Na_2HPO_4 \cdot 12\ H_2O$ and 0.363 Gm. KH_2PO_4 per liter with 100 ml. of 5 per cent phenol added after sterilization.

products were determined, are in agreement with the results presented in table 1. In no instance did it appear that the very small No. 12 beads were any better than the large beads and sand; hence the 4 mm. beads and sand were used for all subsequent work.

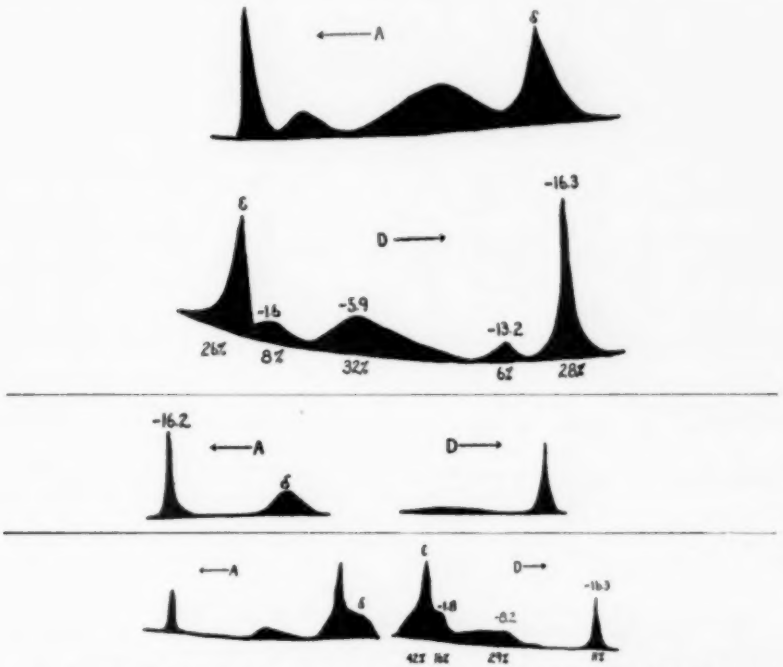


FIG. 1. (Upper) Electrophoretic pattern of a whole extract of tubercle bacilli after 60 minutes at 6.2 volts per cm. in veronal buffer, 0.1 ionic strength at pH 8.6. The mobility of each component, times 10^5 cm^2/volt/sec., is indicated above each component and the percentage of the total area is indicated below the diagram.

FIG. 2. (Center) Electrophoretic pattern of the material adsorbed from a crude extract of tubercle bacilli by calcium phosphate. The pattern was obtained after 20 minutes at 5.7 volts per cm. in veronal buffer, 0.1 ionic strength, at pH 8.6.

FIG. 3. (Lower) Electrophoretic pattern of the supernatant of a crude extract of tubercle bacilli after adsorption with calcium phosphate. The pattern was obtained after 45 minutes at 6.1 volts per cm. in veronal buffer, 0.1 ionic strength, at pH 8.6. The mobility of each component, times 10^5 cm^2/volt/sec., is indicated above each component and the percentage of the total area is indicated below the diagram.

Electrophoretic pattern: The electrophoretic pattern of a crude extract, shown in figure 1, indicates that the whole extract consists of nucleic acid and three other components with lower electrophoretic mobilities. Some neutral substances, such as polysaccharides, also may be present in the delta and epsilon boundaries.

Figures 2 and 3 show the results of a calcium phosphate treatment. Obviously, all of the nucleic acid was not removed by the first calcium phosphate treatment, but, as indicated in table 2, further treatment with calcium phosphate does remove nearly all of the desoxyribonucleic acid. Since the supernatant of the

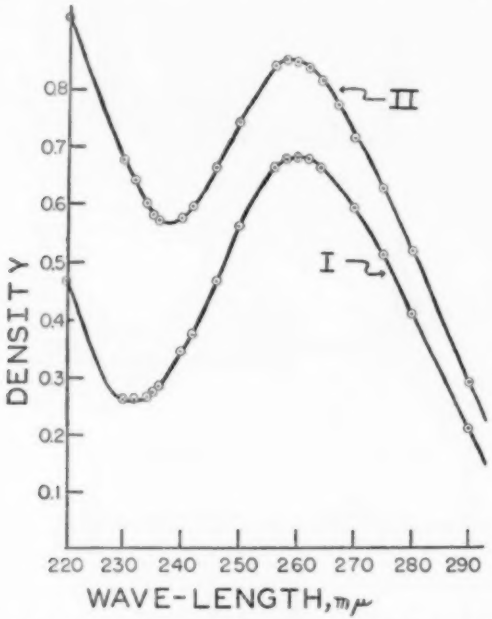


FIG. 4. Ultraviolet absorption of I, pure Hammarsten's thymus nucleic acid and II, the material adsorbed from crude extracts of tubercle bacilli by calcium phosphate.

TABLE 2

Chemical Analysis of Various Preparations

PREPARATION	PERCENTAGE OF DRY MATERIAL		
	Desoxyribonucleic acid	Carbohydrate	Nitrogen
Crude extract	16.5	53	7.5
Fraction adsorbed on calcium phosphate	89.0	11	13.9
Supernatant after calcium phosphate adsorption	0.6	66	6.0

calcium phosphate treatment was observed to have a minimum absorption at 2,600 Å, the total nucleic acid content, too, must be very low. Electrophoretic analysis (figure 3) indicates that the calcium phosphate selectively adsorbs the nucleic acid. The ultraviolet absorption curve of the adsorbed material is also like that produced by pure nucleic acid (figure 4). However, more critical chemical

analyses (table 2) indicate that the preparation contains appreciable amounts of carbohydrate and only about 90 per cent desoxyribonucleic acid.

Biologic activity: The biologic activity of the preparations was tested in tuberculous guinea pigs. As shown in table 3, the supernatant of the calcium phosphate treatment appeared to be the most potent. Therefore, this preparation

TABLE 3

Relative Potencies of Extracts of Tubercle Bacilli and PPD Preparations

PREPARATION	AMOUNT INJECTED γ	AVERAGE DIMENSIONS OF REACTION IN MM.*	
		Test preparation	Standard 0.5 γ PPD-S
TBX-6 Ca precipitate	5	15 x 15 x 2	11 x 12 x 2
	10	15 x 15 x 2	13 x 14 x 2
TBX-6 Ca supernatant	5	23 x 25 x 4	13 x 13 x 2
	10	25 x 30 x 4	10 x 12 x 2
TBX-8 whole extract	5	17 x 15 x 3	10 x 10 x 2
	10	10 x 12 x 1.5	10 x 11 x 1
TBX-11 whole extract	5	20 x 20 x 3	15 x 15 x 2
	10	died	
TBX-9 Ca precipitate	10	15 x 17 x 2	15 x 15 x 2
TBX-9 Ca supernatant	10	15 x 17 x 2	15 x 15 x 2
PPD 70-2	5	16 x 17 x 3	10 x 10 x 2

* Reactions of guinea pigs to intradermal test 1½ months after infection with the DT strain of *M. tuberculosis*.

TABLE 4

A Comparison of Reactions to Increasing Amounts of Tuberculin and Extracts of Tubercle Bacilli

AMOUNT INJECTED (γ)	AVERAGE DIMENSIONS OF REACTION IN MM.*	
	TBX-6 Ca Supernatant†	PPD-S
0.01	3 x 3 x .5	not tested
0.1	11 x 13 x 1.5	16 x 16 x 2
0.5	16 x 17 x 2	16 x 17 x 2
1.0	17 x 18 x 2	not tested

* Reactions of guinea pigs to intradermal tests seven months after infection with DT strain of *M. tuberculosis*.

† Supernatant after adsorption of crude extract with calcium phosphate.

was re-tested at more appropriate concentrations. A summary of the results is presented in table 4. It is true that such a small number of observations are statistically unreliable, but it may be valid to conclude that the potency of this relatively crude preparation extracted from the organism does not differ too greatly from that of a potent preparation, PPD-S[9].

[9] We are indebted to Dr. Florence Siebert for the standard tuberculin, PPD-S.

DISCUSSION

As has been mentioned previously, the principal reason for attempting to extract the native proteins from young tubercle bacilli is to obtain a more specific tuberculin. An additional advantage of working with native, rather than degraded, proteins is that undenatured proteins may be more easily fractionated by chemical means into better defined and more homogeneous preparations. Seibert (2) states that a large number of proteins exist in tuberculin, especially in heated preparations which differ only slightly from each other, and consequently cannot be separated easily. Although evidence presented by Bevilacqua and McCarter (16, 17) indicates that only two distinct proteins are present, in addition to the polysaccharide and nucleic acid, they have separated unheated culture filtrates into 14 fractions. All of their fractions contained protein, varying from 7 to 94 per cent of the total weight. Because autolysis is not a simple chemical change, there is little reason to expect clearly defined homogeneous end products. There may be numerous intermediate degradation products, which would lead to an entire spectrum of proteins; therefore it is believed that by extracting the whole organism one may obtain considerably more homogeneous materials.

Admittedly, the procedure that was employed is not without its faults, but it does have two principal advantages over the methods which have been used by previous investigators. No special treatment of the bacilli is required, such as drying or ether extraction, and it offers the maximum possible protection for the operator.

The rationale for employing ethyl ether in the phosphate buffer extraction of the disintegrated bacilli is that a small amount of ether will rupture the bonds between the protein and the insoluble lipid. Craigie (18), in the application of the ethyl ether method of purifying typhus rickettsiae, discussed some of the means of controlling the process of separating the lipoidal material from the more hydrophilic components. Ether has been used by other investigators in the purification of viruses, as well as rickettsiae. Because ethyl ether is an excellent fat solvent, it is not surprising that the forces binding the lipid-protein complex were overcome, leaving the protein portion in the aqueous phase. Without adding ether, the amount of water-soluble material extractable from the disintegrated bacteria was negligible; therefore, the proteins probably were bound to the lipids of the cell, which formed an insoluble complex.

Treatment of the crude extract with calcium phosphate produces some interesting changes in the relative composition of the electrophoretic components. In a comparison of figures 2 and 3 with figure 1, it may be seen that a summation of figures 2 and 3 does not produce a composite pattern similar to that obtained with the whole crude extract. After the calcium phosphate treatment, the component which originally had a mobility of -13.2×10^{-5} cm^2/sec/volt was completely absent from either the supernatant or the precipitate. Other changes are apparent, particularly in the relative concentration of the various components. One explanation of the change is that some of the components observed in the crude extract are not pure proteins, but are nucleoproteins; the phosphate

treatment dissociates the complex into nucleic acid and proteins. Pure proteins normally do not have a mobility as great as the second component, −13.2; therefore this component must be a nucleoprotein. The complete disappearance of the fast component after the calcium treatment would occur if the bonds between the protein and nucleic acid were relatively labile, and were quantitatively ruptured by a low concentration of calcium. The protein component would then have a lower mobility, and the nucleic acid would be included in the leading component. Because the same changes have been observed in subsequent experiments, it is likely that the observed changes are a direct result of the calcium phosphate treatment.

The observed viscosity of the crude extract of the tubercle bacilli was much higher than that reported by Chargaff (4) for the nucleoproteins he extracted with borate buffer from avian tubercle bacilli. He reported a specific viscosity ($\eta_{sp} = \eta/\eta_0 - 1$) of 0.14 for an 0.28 per cent solution of the nucleoprotein. In contrast with his observations, an 0.25 per cent solution of the crude material extracted with phosphate buffer and ether had a specific viscosity of 1.47 at 20°C. Exact measurements were not made of the nucleic acid which was adsorbed from the crude extract by calcium phosphate, but it has a viscosity considerably greater than 1.5.

An ethanol fractionation of the crude extract was attempted but, because of the high viscosity, such a procedure was not found to be feasible. If the solution were diluted to a workable viscosity, insignificant amounts would precipitate; and if sufficient concentration of material was used, the viscosity interfered directly with the removal of precipitates. However, it might be possible to employ other solvents, such as isopropyl alcohol, which Alberty and Heidelberger (19) found satisfactory for the fractionation of viscous preparations of pneumococcus polysaccharides. In view of the success experienced with the adsorption of nucleic acid by calcium phosphate, however, it would seem advisable to remove the nucleic acid before attempting any type of separation of the proteins and polysaccharides. Seibert (1) has outlined a fractionation procedure which might be applicable to the tubercle extract. However, a procedure is being sought which will avoid subjecting the proteins to acidic solutions. The tuberculin activity is stable to dilute acids, but many proteins are known to be denatured at pH 3.5 to 4.

No attempt has been made to determine whether the materials extracted from the bacilli are more specific than OT or PPD in detecting those animals infected with the mammalian type of tubercle bacilli. Before such studies are undertaken, it would be necessary to prepare similar extracts from cultures of the avian strain of tubercle bacilli. If fractionation of the crude extracts beyond the preliminary removal of the nucleic acid portion is not obtained readily, attempts will be made to determine the specificity of the whole extract, even though it is desirable to work with pure proteins. As mentioned in the introduction, Seibert (2) has isolated substances from unheated culture filtrates which are more potent in eliciting the tuberculin reaction than her potent standard, PPD-S, but an increase in potency does not necessarily mean a comparable increase in

specificity. It is generally true, however, that the more native proteins have the greater biologic specificity.

McCarter and Watson (20) have demonstrated that the intracutaneous activity of a tuberculin is directly correlated with antigenicity, and that the size of the molecule alone does not determine its antigenicity. Apparently some grouping within the molecule is responsible for the antigenicity and skin activity. However, because a nonantigenic preparation has been obtained with high tuberculin activity (2), the two properties of the protein molecule are not necessarily interdependent. Raffel (21) has stated that an ideal tuberculin would be one in which the proteins were of known concentration, known skin reactivity, and nonantigenic; but it is obvious that such a preparation also should be specific for the type of tuberculosis, either mammalian or avian.

A comparison of the reactions elicited by the various preparations (tables 3 and 4) indicates that the activity of the material extracted from the whole organism is fairly comparable with that of the standard tuberculin. Because the size of reaction is not directly proportional to the amounts of tuberculin injected, most of the results are only semi-quantitative indications of the relative activity. Although none of the preparations obtained by the extraction of the tubercle bacilli is more potent than PPD, there is a possibility that a substance can be isolated which has a much greater activity than PPD-S. The presumptive evidence for a more potent tuberculin is found in the correlation of the electrophoretic studies and the biologic activity. As shown in table 3, the potency of either of the calcium phosphate precipitates is about equal to whole crude extracts, and the supernatant of only one separation was appreciably more active than whole extracts. If these observations are correlated with the electrophoretic analysis of the whole extract and the two fractions which were obtained by adsorption with calcium phosphate, it may be seen that the activity exhibited by the material adsorbed onto the calcium phosphate is due to some component which is present in amounts too small to be shown by electrophoresis. If the nucleic acid were the active principle, one would expect the precipitate, which contained a higher percentage of nucleic acid, to exhibit a much greater potency than the supernatant; but such is not the case. It is possible, also, that the delta and epsilon boundaries contain components which can elicit a reaction, but this is unlikely, since the polysaccharides, as well as nucleic acid, have been shown to possess no tuberculin activity except for the amount of contaminating proteins (1, 20). Continued electrophoresis of the calcium phosphate precipitate (figure 2) did not reveal any other components migrating out of the delta boundary, even after an additional 40 minutes. Only further investigation and fractionation of the extract will determine whether an extremely potent protein is present in an extract of young tubercle bacilli. It remains to be demonstrated that an increased potency of the tuberculin proteins is paralleled by an increased specificity of action.

SUMMARY

An apparatus has been described which is suitable for the disintegration of tubercle bacilli. The bacterial cell walls are ruptured by vigorous shaking of a paste of the organisms with glass beads.

A phosphate buffer, pH 7.3, was used for the extraction of the cell debris after shaking, and ethyl ether was found to be necessary to obtain satisfactory yields.

To minimize denaturation of proteins, the entire shaking and extraction process was carried out at as low a temperature as possible, particularly in the presence of ether.

Electrophoretic analyses indicate the presence of nucleic acid and three other slower components, at least one of which is presumed to be a nucleoprotein. Nucleic acid can be adsorbed selectively from the crude whole extract by calcium phosphate precipitated *in situ*.

The material extracted from the tubercle bacillus has a potency comparable to the PPD preparations when tested in tuberculous guinea pigs. Evidence is presented which indicates that a substance more potent than PPD is present in the water-soluble extract.

The advantages of isolating undenatured proteins were discussed, with particular reference to the possibility of obtaining a more specific agent for tuberculin testing.

SUMARIO

Extracción de las Proteínas y Otros Componentes del Bacilo Tuberculoso, con Algunas Observaciones Relativas a sus Propiedades Químicas y Biológicas

El aparato descrito se presta para la desintegración de los bacilos tuberculosos, quebrándose las paredes de las células bacterianas mediante la enérgica agitación de una pasta de los microbios con cuentas de vidrio.

Para la extracción de los desechos celulares después de la agitación, se empleó un regulador de fosfato, pH 7.3, resultando necesario el uso de éter etílico para obtener rendimientos satisfactorios.

Para reducir al mínimo la desnaturalización de las proteínas, todo el procedimiento de agitación y extracción fué ejecutado a la temperatura más baja posible, en particular en presencia de éter.

Los análisis electroforéticos indican la presencia de ácido nucleico y de otros tres componentes más lentos, por lo menos uno de los cuales se presume que es una nucleoproteína. El ácido nucleico puede ser adsorbido selectivamente del extracto íntegro crudo con fosfato de calcio precipitado *in situ*.

El material extraído del bacilo tuberculoso muestra una potencia comparable a la de las preparaciones de PPD al ser ensayado en cobayos tuberculosos. Preséntanse datos indicativos de que, en el extracto hidrosoluble, hay presente una sustancia más potente que PPD.

Discútense las ventajas de aislar proteínas no desnaturalizadas, y en particular la posibilidad de obtener un agente más específico para la comprobación con tuberculina.

Acknowledgment

It is a pleasure to acknowledge the excellent cooperation and interest of Professor J. W. Williams and the use of the laboratory facilities so generously made available by him.

REFERENCES

(1) Seibert, F. B.: The isolation of three different proteins and two polysaccharides from tuberculin by alcohol fractionation: Their chemical and biological properties, Am. Rev. Tuberc., 1949, *59*, 86.

(2) Seibert, F. B.: The chemistry of tuberculin, Chem. Rev., 1944, *34*, 107.

(3) Heidelberger, M., and Menzel, A. E. O.: Protein fractions of the human strain (H-37) of the tubercle bacillus, J. Biol. Chem., 1934, *104*, 655.

(4) Chargaff, E., and Saidel, H.: On the nucleoproteins of avian tubercle bacilli, J. Biol. Chem., 1949, *177*, 417.

(5) Dubos, R. J., and Middlebrook, G.: Media for tubercle bacilli, Am. Rev. Tuberc. 1947, *56*, 334.

(6) Anderson, A. W.: The proteolytic and lipolytic activity of several strains of *Lactobacillus casei*, Thesis, University of Wisconsin, Madison, 1947.

(7) Curran, H. R., and Evans, F. R.: The killing of bacterial spores in fluids by agitation with small inert particles, J. Bact., 1942, *43*, 125.

(8) King, H. K., and Alexandria, H.: The mechanical destruction of bacteria, J. Gen. Microbiol., 1948, *2*, 315.

(9) Tiselius, A.: A new apparatus for electrophoresis of colloidal mixtures, Tr. Far. Soc., 1937, *33*, 524.

(10) Alberty, R. A.: An introduction to electrophoresis: I. Methods and calculations, J. Chem. Educ., 1948, *25*, 426.

(11) Watson, D. W., Cromartie, W. J., Bloom, W. L., Kegeles, G., and Heckly, R. J.: Studies on infection with *Bacillus anthracis:* III. Chemical and immunological properties of the protective antigen in crude extracts of skin lesions of *B. anthracis*, J. Infect. Dis., 1947, *80*, 28.

(12) Seibert, F. B.: Personal communication, 1948.

(13) Dische, Z.: Über einige neue charakteristische Farbreaktionen der Thymonukleinsäure und eine Mikromethode zur Bestimmung derselben in tierischen Organen mit Hilfe dieser Reaktionen, Mikrochemie, 1930, *8*, 4.

(14) Kabat, E. A., and Mayer, M. M.: Experimental Immunochemistry, Charles C Thomas, Springfield, Illinois, 1948.

(15) Morris, D. L.: Quantitative determination of carbohydrates with Dreywood's anthrone reagent, Science, 1948, *107*, 254.

(16) Bevilacqua, E. B., and McCarter, J. R.: The proteins in unheated culture filtrates of human tubercle bacilli: I. Fractionation and determination of physical-chemical properties, J. Exper. Med., 1948, *87*, 229.

(17) McCarter, J. R., and Bevilacqua, E. B.: The proteins in unheated culture filtrates of human tubercle bacilli: II. Determination of serological properties, J. Exper. Med., 1948, *87*, 245.

(18) Craigie, J.: Application and control of ethyl-ether-water interface effects to the separation of rickettsiae from yolk sac suspensions, Canadian J. Research, E, 1945, *23*, 104.

(19) Alberty, R. A., and Heidelberger, M.: Fractionation and physical-chemical studies of a commercial preparation of the specific polysaccharide of Type I pneumococcus, J. Am. Chem. Soc., 1948, *70*, 211.

(20) McCarter, J. R., and Watson, D. W.: The relationship of the antigenicity, physical-chemical properties, and polysaccharide-content of tuberculins to their intracutaneous activity, J. Immunol., 1942, *43*, 85.

(21) Raffel, S.: Tuberculin and its derivatives, Stanford M. Bull., 1945, *3*, 24.

THE RESULTS OF THE TREATMENT OF ACTIVE MINIMAL PULMONARY TUBERCULOSIS WITH "MODIFIED" BED REST

A Statistical Analysis of 289 Patients Followed for Seven Years after Discharge from Trudeau Sanatorium[1]

ROGER S. MITCHELL AND JACK R. KNUDSON

(Received for publication December 9, 1949)

INTRODUCTION

The problem of the proper treatment of minimal pulmonary tuberculosis is of growing importance because of the increasing number of minimal lesions being discovered by routine and mass roentgenography (1). While bed rest has been the keystone of the treatment of this disease, there is much disagreement as to the *degree* and *duration* of bed rest which should be employed (2–7). "Strict" bed rest seems to have the most support (8–15). "Modified" bed rest has been preferred by others (16, 17). Finally, a combination of "rest and exercise" has also been recommended (18).

"Modified" bed rest is defined in this report as from twenty to twenty-one hours per day reclining in bed or on a chaise longue, with meals eaten in an adjoining room, and full bathroom privileges. Riding or walking to other buildings for examinations was permitted, but no other outdoor exercise was allowed. "Strict" bed rest is defined as twenty-three and one-half to twenty-four hours per day in bed, with the use of bedpans, stretchers for transportation to laboratories, and the like. Twenty-two of the patients studied were so treated for one to three months before admission to Trudeau Sanatorium but, because of its very limited use, this "strict" bed rest was regarded as "modified" bed rest for the purposes of this study.

MATERIALS AND METHODS

This study was based upon a review of the records of all patients admitted to Trudeau Sanatorium between January 1, 1930 and December 31, 1940. In 577 (22 per cent) of the 2,612 patients admitted in these eleven years, the pulmonary lesions were classified as minimal at the time of admission to the sanatorium.

These 577 patients were then studied clinically and roentgenographically from the time of admission through their sanatorium residence and the ensuing years until 1948. Serial roentgenograms were available to the writers in all but 26.

The purpose of the study was to observe the results of treatment of uncomplicated active minimal pulmonary tuberculosis. Certain of the 577 original cases were excluded (table 1) for the following reasons: (a) 24 patients in retrospect did not exhibit conclusive evidence of tuberculosis, and were, in most instances, shown by subsequent events to have been incorrectly diagnosed; (b) 54 had advanced rather than minimal disease on admis-

[1] This study was supported in part by the Edward L. Trudeau Foundation and by a grant from the Lawrason Brown Memorial Fund.

sion, in the authors' opinion; (c) 76 had pleural effusion, either with or without minimal pulmonary infiltration; (d) 5 had a calcified primary complex only; (e) 11 cases were complicated by frank bronchial disease; and (f) in 11 cases the chief problem was some form of extrapulmonary tuberculosis. Thirty additional cases were excluded because advanced disease was found at some time prior to admission.

Finally, 59 patients were excluded because the lesions were classified as "inactive" on the basis of the roentgenographic and bacteriologic criteria outlined below, in spite of the presence of suggestive symptoms in 45. The abnormal roentgen shadows in these 59 patients were calcific in 9, stringlike in 29, mixed calcific and stringlike in the other 21; and these lesions remained unchanged during sanatorium residence in all instances.

TABLE 1

Reclassification of Series

The authors' reclassification of the 577 patients differed from the original admission classification of minimal disease as follows:

	NUMBER OF CASES	PER CENT OF TOTAL
Tuberculosis		
Pulmonary only		
Minimal active	307	53
Minimal inactive	59	10
Moderately advanced on admission	54	9
Moderately advanced before admission (minimal on admission)	30	5
Primary complex (calcified)	5	1
Extrapulmonary plus minimal pulmonary		
Bronchial disease	11	2
Pleurisy with effusion	61	11
Other	11	2
Pleurisy with effusion but with no discernible pulmonary infiltration	15	3
Total tuberculosis	553	
No tuberculosis	24	4
Total	577	100

The remaining 307 cases, exhibiting nodular or fluffy densities, were then regarded as "active," whether or not the shadows appeared "inactive" or "stable" on serial roentgenograms.

Sputum was considered "positive" when the clinical record revealed one or more sputum or gastric cultures positive for *M. tuberculosis*, or one bacillus count of Gaffky II or higher on a smear of concentrated sputum collected over a 50-hour period. The finding of no more than one to four acid-fast rods after a 20-minute search (Gaffky I) was arbitrarily disregarded as conclusive evidence of "positive" sputum for the purposes of this study. No direct smears of unconcentrated sputum, smears of gastric contents, or guinea pig inoculations were employed in this series. Sputum cultures were not regularly made until 1935; gastric cultures, not until 1939.

The results of all cases were then determined solely from the standpoint of reactiva-

tion of disease as "good," "poor," or "nonevaluable." A "good" result was defined as clinical and roentgenographic improvement, return to full-time employment, without reactivation of disease for at least *seven years* following discharge from the sanatorium.[3]

A very minor or questionable increase in infiltration, not soon followed by a more definite increase, was not in itself considered sufficient evidence of a "poor" result; this occurred in 15 cases (figure 6).

A "poor" result was defined as either *progression* or *relapse* of pulmonary disease. "Progression" was defined as the development of a cavity or a significant spread of disease on the routine chest roentgenogram at any time *before* the patient's return to full employment. "Relapse" was defined as any reactivation of disease which led to a resumption of treatment either at home or in a sanatorium *after* return to full employment within seven years following discharge. A seven-year observation period was chosen because, by 1948–1949, seven years or more had elapsed from the time of discharge of the last patients admitted in 1940.

A case not followed for seven years was considered *nonevaluable*, provided no reactivation had occurred up to the time contact was lost. Eighteen of the 307 patients with active minimal disease were nonevaluable for this reason, 3 because of death due to nontuberculous causes in less than 7 years. This left 289 cases which were subjected to a statistical analysis.

RESULTS

All results were tested for statistical significance. The standard error of the difference between two percentages, two means, or two medians was computed with standard formulas (19). It has been shown that when the ratio: $\frac{\text{Observed Difference}}{\text{Standard Error of the Difference}}$ is 3.0 or more, there is one or less chance in 370 that the observed difference could be due only to chance, a so-called *significant* difference. When this ratio is between 2.0 and 3.0, there is one or less chance in 20 that the observed difference could be due to chance; such a finding was considered in this study as *probably significant*. When this ratio is less than 2.0, there may be one or less chance in 10 that the observed difference could be due only to chance, i.e., a difference which is *not significant*.

The results fell into three parts.

The Over-all Incidence of Reactivation and the End Results

The incidence of reactivation occurring in the entire series after reclassification is recorded in table 2. The total absence of reactivation in the 59 "inactive" cases, in spite of the presence of suggestive symptoms in 45 (including hemoptyses in 10), was rather striking. A similar observation has been made by others (10, 20, 21) with one dissent (22). The balance of the study is an analysis of the 289 patients with active minimal disease with whom contact was maintained for seven years or more after discharge (figure 1). The cumulative reactivation rate

[3] The number of sputum smears and cultures was inadequate in some cases, especially in the earlier years; hence a "negative" sputum on discharge is not included as one of the criteria of a "good" result. In fact, the last sputum prior to discharge was "positive" in 17 cases found to have achieved a "good" result.

TABLE 2

Incidence of Reactivation Observed in All Patients Originally Classified as Having "Minimal" Tuberculosis on Admission, but after Reclassification by the Writers

WRITERS' RECLASSIFICATION OF 577 MINIMAL CASES	TOTAL	CASES FOLLOWED FOR 7 YEARS OR MORE AFTER DISCHARGE		
		Total	Reactivation within 7 years	
			Number	Per cent
Tuberculosis				
Minimal active	307	289	107	37
Minimal inactive	59	59	0	0
Moderately advanced on admission	54	52	27	52
Minimal on admission but previously moderately advanced	30	28	11	40
Pleurisy with effusion	76	72	23	32
Endobronchial disease	11	11	6	54
All other tuberculosis	16	—	—	—
Total—Tuberculosis	553	—	—	—
No tuberculosis	24			
Total originally classified as "minimal"	577			

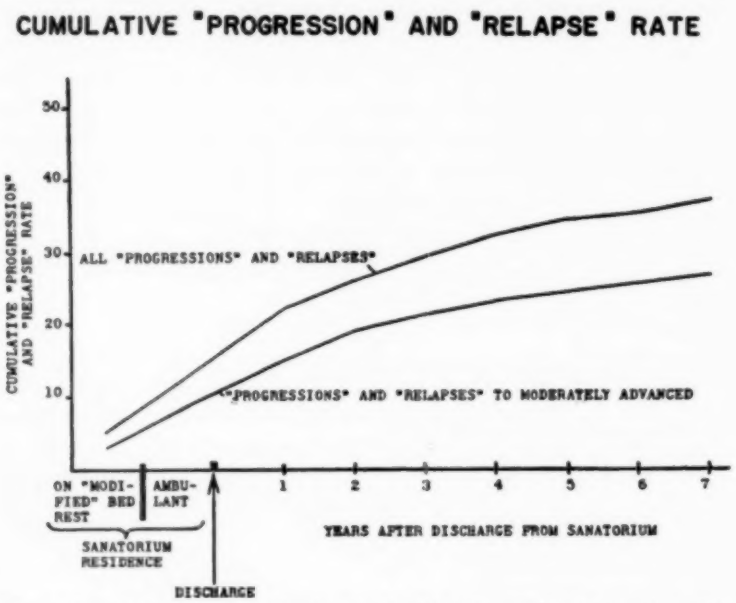


FIG. 1. Cumulative 7-year reactivation rate in 289 patients treated for active minimal pulmonary tuberculosis with "modified" bed rest. (No more than one reactivation is counted in each case.)

in these 289 cases was 37 per cent. The upper curve includes all reactivations (37 per cent) while the lower curve includes only those cases known to have progressed at any time beyond the minimal stage of the disease (26 per cent).

Bobrowitz, Hurst, and Martin (9) have reported a 42 per cent cumulative progression rate in one to seven years in a series of 220 minimal cases treated with an average of six months' sanatorium rest; this series, however, included 34 per cent non-white individuals. Reisner (23) found a 28 per cent "frank progression" rate in 130 patients with minimal *newly acquired* lesions given treatment which he considered inadequate; this series also is not comparable to the present series because of the inclusion of a number of non-white individuals, and because the lesions were all newly acquired. Orrego-Puelma and Grebe (24) reported a 24 per cent cumulative reactivation rate in a two-year follow-up of 100

TABLE 3

Present Status of 307 Patients with Active Minimal Tuberculosis 7 to 18 Years after Discharge from Trudeau Sanatorium

	NUMBER OF CASES	PER CENT
Well and working in 1948 to 1949	244	79
Well and working 7 years or more after discharge, but contact then lost	16	5.5
Contact lost less than 7 years after discharge; working and apparently well at the time	13	5
Dead of nontuberculous causes 2 to 12 years after discharge; tuberculosis stable at death	10	3
Dead of nontuberculous causes, within one year of discharge; tuberculosis active	2	0.5
Dead of tuberculosis	9	3
Chronic active tuberculosis under treatment in 1948 to 1949	13	4
Totals	307	100

South American patients. Reisner and Downes (21) reported a 49 per cent cumulative progression rate in 291 white patients, followed for five years, who had very little treatment.

From figure 1 it may also be seen that in 60 per cent of the patients with any reactivation, the phenomenon had appeared by the end of the first year following discharge from the sanatorium. This approximates the experience of others in similar series of patients (8, 9, 25).

Attention is also called to the fact that in 9 cases the first reactivation occurred *more* than seven years after discharge. These 9 cases were arbitrarily classified as "good" results in making the statistical analyses.

The present status of the entire series of 307 cases of active minimal pulmonary tuberculosis, seven to eighteen years after discharge from the sanatorium, is shown in table 3. Although contact is now lacking in 10.5 per cent, there was less than a seven-year follow-up in only 5 per cent. Other writers have reported

90 per cent "able to work" five years after stopping treatment (26), 75 per cent "working" five to seventeen years after discharge (27), and 87 per cent "in a good or arrested condition" three years or more after discharge (28).

Table 4 summarizes the treatment given for all reactivations both during initial sanatorium resisdence and after discharge. Including all "progressions" of disease in the sanatorium, 83 patients are known to have been treated for one reactivation, 26 for two, 6 for three, and one for four reactivations up to the present time. Six patients have had thoracoplasty; none has had pulmonary resection.

TABLE 4

Type of Treatment Used for All Known Reactivations Occurring in 307 Cases of Active Minimal Tuberculosis

TYPE OF TREATMENT	CASES SHOWING REACTIVATION WITHIN 7 YEARS FOLLOWING DISCHARGE	CASES IN WHICH INITIAL REACTIVATION OCCURRED MORE THAN 7 YEARS AFTER DISCHARGE
Bed rest only	55	4
Phrenic paralysis	12	1
Phrenic and pneumoperitoneum	1	0
Phrenic, then pneumothorax	4	1
Phrenic, pneumothorax, then thoracoplasty	1	0
Phrenic, then thoracoplasty	1	0
Pneumothorax	24	1
Thoracoplasty	3	1
Extrapleural plombage	0	1
Unknown	6	0
Totals	107	9

Thirty-three patients are known to have had two or more reactivations.

The Relationship of Various Clinical Features and of the Duration of Treatment to Results

The 289 patients followed for seven years or more were analyzed statistically. The age range was from 15 to 61 years, with a mean of 26 and a median of 27 years. There were 145 males and 144 females.

The *age and sex* distribution in figure 2 shows an improving prognosis of probable significance with passing years in females. Age alone, exclusive of sex, however, showed differences which were not significant. An improvement in prognosis with increasing age has been reported in other studies of minimal disease (20, 21). Age, however, has been recently reported by Reisner (23) as having no bearing on late results in his series of patients with newly acquired lesions, most of whom, however, had received little or no treatment.

Results in males were not significantly better than in females, although males have been previously reported as having a better prognosis (26).

This series was composed predominantly of individuals of pure or mixed Northern European descent, with too small a number of Southern Europeans,

Slavs, and Orientals to permit a comparison of results in these *racial groups*. There were no Negro patients in this series.

The effect of *relative age of disease* on results is demonstrated in figure 3. The presumably recent lesions were observed to follow a significantly more unstable

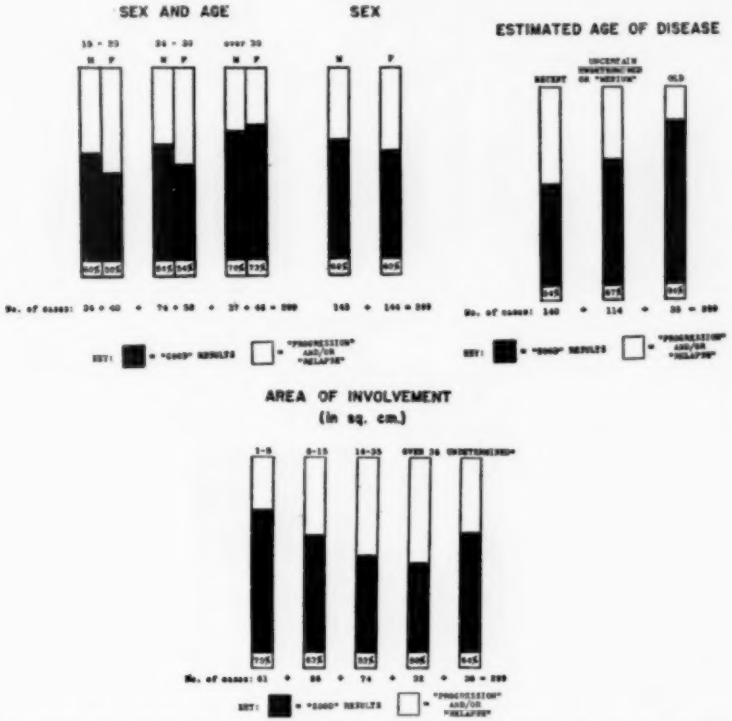


FIG. 2. (Left) Relationship of sex and age to the incidence of reactivation during treatment and for 7 years following discharge of 289 patients treated for active minimal tuberculosis with "modified" bed rest.

FIG. 3. (Right) Relationship of estimated age of disease to incidence of reactivation.

FIG. 4. (Bottom) Relationship of average extent of lung involvement on the flat chest film to incidence of reactivation.

* First film technically poor or missing.

course than the definitely old lesions; there was also a probably significant difference when recent lesions were compared with lesions of medium or uncertain duration. The estimated age of disease was based upon the duration and nature of symptoms and the character of the roentgen shadows in serial films, including many taken some months or even years *before* admission. In deciding that a lesion was old, attention was paid in particular to evidence of pulmonary con-

traction, stringlike and calcific densities, and patches of emphysema. A case was classified as of medium duration when the various considerations placed it somewhere between recent and old, or when the age of the disease was not clear from the evidence.

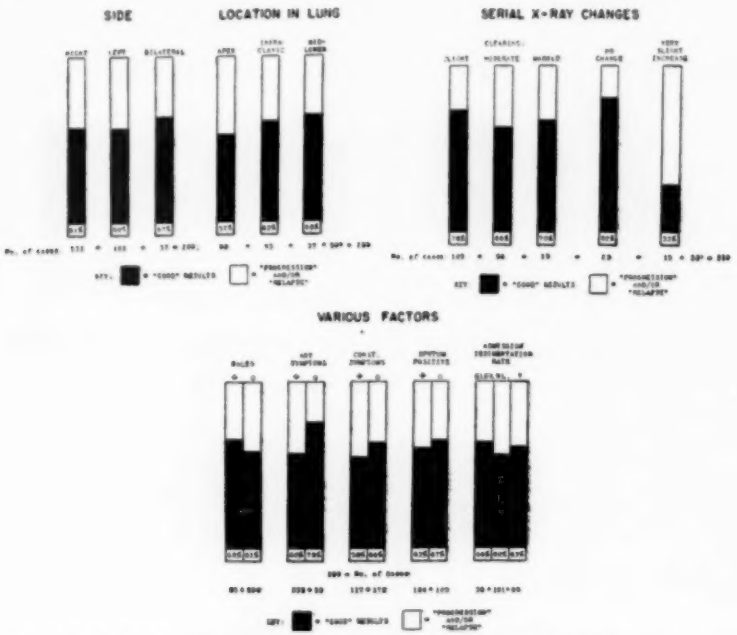


FIG. 5. (Left) Relationship of location of disease to incidence of reactivation.

* Cases with multiple location in one lung	2
Cases with bilateral lesions	57
Total cases excluded from this study	59

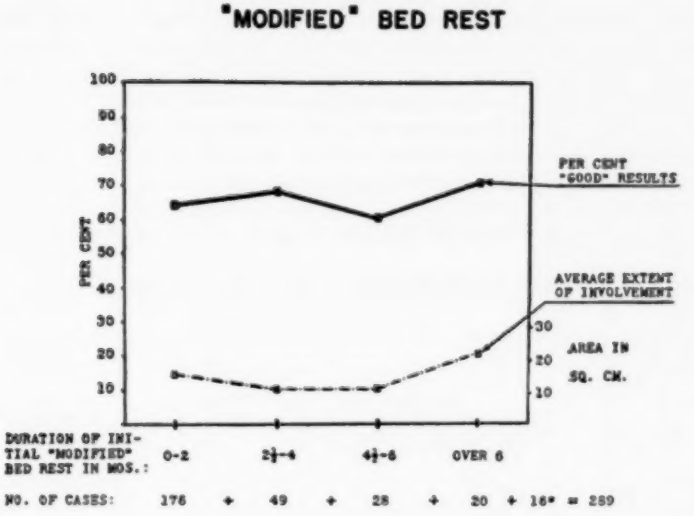
FIG. 6. (Right) Relationship of serial roentgenographic changes during sanatorium residence to incidence of reactivation.

* 32 cases excluded because of *progression* during sanatorium residence.

FIG. 7. (Bottom) Relationship of various factors to incidence of reactivation.

Extent of pulmonary involvement: There was a direct correlation between results and the average extent of pulmonary involvement as measured in square centimeters on the flat chest film (figure 4). Of the differences between results in small lesions of 1 to 5 sq. cm. on the one hand, and the larger lesions (6 to 15 sq. cm., 16 to 35 sq. cm., and 36 sq. cm. or over) on the other, the latter two differences were found to be probably significant.

Location of lesion: The relationship of location of the lesion to results is seen



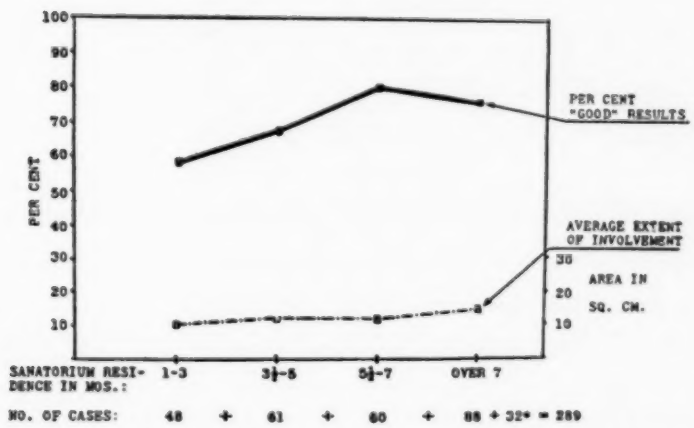


FIG. 8. (Top) Relationship of duration of initial "modified" bed rest to incidence of reactivation.

* 16 cases excluded because *progression* occurred while still on "modified" bed rest.

FIG. 9. (Bottom) Relationship of duration of sanatorium residence to incidence of reactivation.

* 32 cases excluded because *progression* occurred while still in residence at the sanatorium.

in figure 5. These differences proved to be insignificant. Location of the disease has previously been reported to have no bearing on late results (21, 22).

Change on serial roentgenograms: Lesions which showed no change on serial roentgenograms during sanatorium residence presented a significantly more favorable prognosis than those showing slight or questionable increase of infiltration (figure 6). There was also a more favorable prognosis of probable significance when lesions showing any degree of clearing were compared to the latter group. The rapidity and degree of clearing during sanatorium residence, however, had no significant bearing on results. The 32 cases exhibiting progression during sana-

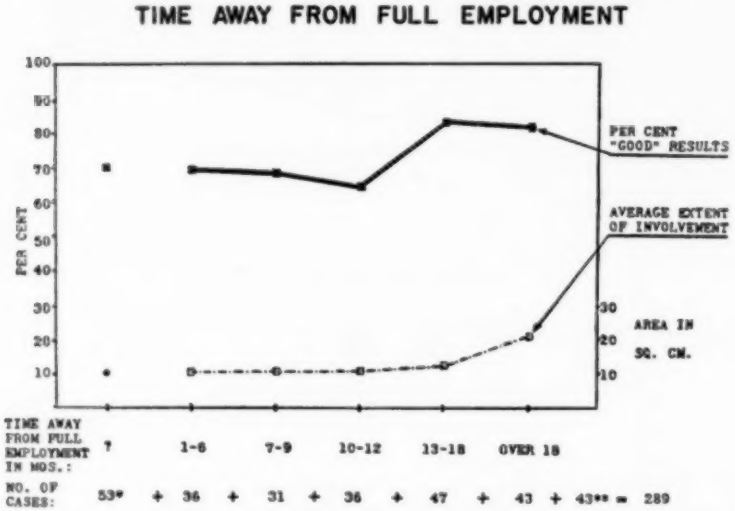


FIG. 10. Relationship of time away from full employment to incidence of reactivation.
* Inadequate data on time away from full employment.
* * 43 cases excluded because *progression* occurred before return to full employment.

torium residence were necessarily excluded from this figure because reactivation often occurred before prior data on serial roentgenographic changes were available.

Miscellaneous factors: The relationship of various other factors to results is presented in figure 7. The presence or absence of rales did not affect the prognosis. The absence of symptoms before admission was found to be a favorable prognostic sign of probable significance. The erythrocyte sedimentation rate (Cutler) on admission was found to have no bearing on late results. A rather surprising finding was that results were not related to the finding of "positive" sputum at some time during sanatorium residence. Sputum was found "positive" in 64 per cent of the 289 cases.

Duration of initial "modified" bed rest: The incidence of "good" results is plotted

against the variations in duration of initial "modified" bed rest in figure 8. The duration of rest actually used in each case includes that received immediately before admission. In computing the mean duration of "modified" bed rest, 16 cases, in which *progression* occurred before completion of "modified" bed rest, were excluded, since "modified" bed rest was prolonged in these cases because of the *progression*. The duration of "modified" bed rest for the other 273 patients ranged from two weeks to thirteen months, with a mean of two months. There

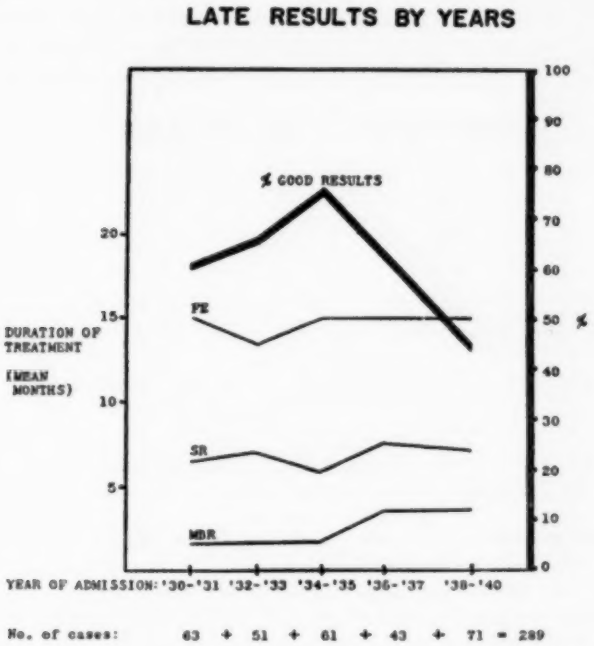


FIG. 11. Freedom from reactivation related to the year of admission and to the average (mean) duration of "modified" bed rest (MBR), sanatorium residence (SR) and total time away from full employment (FE) in 289 cases of active minimal tuberculosis.

was no significant difference in the mean duration of "modified" bed rest between those having later reactivation and those who remained well for the next seven years.

Duration of sanatorium residence and the total time spent away from full employment: Figures 9 and 10 are similar to figure 7, except that duration of sanatorium residence and the total time spent away from full employment, instead of duration of "modified" bed rest, were plotted against results. In figure 9, 32 patients in whom *progression* of the lesions occurred before termination of sanatorium

residence were necessarily excluded since the sanatorium residence of these patients was doubtless prolonged because of the *progression*. The duration of sanatorium residence for the other 257 patients ranged from one to 20 months, with a mean of 6.9 months. The mean duration of sanatorium residence was 7 months for those with "good" results, and 6.2 months for those whose initial reactivation occurred after discharge from sanatorium treatment, a probably significant difference. In addition, it was found that the incidence of later reactivation in patients spending more than 5 months at the sanatorium was less to a probably significant degree than among those spending 5 months or less.

Figure 10 shows a probably significant difference between results in patients spending more than one year away from full employment and those spending

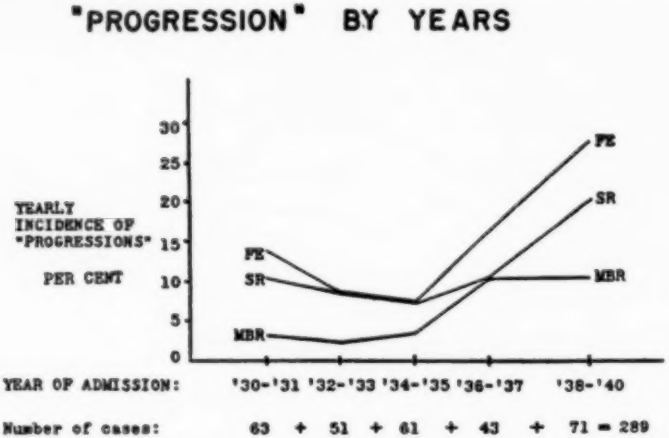


FIG. 12. Incidence of *early* reactivation of disease occurring in 289 patients with active minimal tuberculosis while still being treated with "modified" bed rest (MBR), while still resident in the sanatorium (SR) and at any time prior to return to full employment (FE), related to the year of admission.

one year or less. This was true in spite of a probably significant rise in the average (median) extent of involvement in those remaining away from full employment longer. Forty-three patients in whom *progression* occurred before return to full employment were necessarily excluded, since the time they were away from full employment was doubtless prolonged because of the *progression*. The time away from full employment for the other 193 patients on whom such data were available ranged from 3 to 65 months, with a mean of 20 months. The mean time away from full employment was 16 months for those with "good" results, and 12.7 months for those who had reactivation for the first time after return to full employment, a probably significant difference. The observation that time away from full employment is directly related to incidence of reactivation has been previously reported (25).

Increase in Incidence of Reactivation in Patients Admitted in 1936 to 1940 as Compared with Those Admitted in 1930 to 1935

The incidence of reactivation in relation to the year of admission is shown in figure 11. It is at once apparent that results were notably (and probably significantly) less favorable in those patients admitted in 1936 to 1940 than in those admitted in 1930 to 1935. This difference is more striking in view of the significant increase in the mean duration of initial "modified" bed rest, from 1.5 to 3 months in the patients admitted during the years 1936 to 1940. Meanwhile, the mean duration of sanatorium residence and time away from full employment in these two groups of patients showed no significant change.

Further comparison of these two groups of patients revealed that 48 per cent of initial reactivations in the 1936 to 1940 patients occurred early or before return to full employment, while only 34 per cent of initial reactivations in the patients admitted in 1930 to 1935 were early in the same sense. This difference was found to be probably significant. The incidence of these early reactivations in relation to the year of admission is shown graphically in figure 12.

DISCUSSION

The change in incidence and timing of reactivation exhibited in figures 11 and 12 suggested that a change had occurred in the type of case being treated in 1936 to 1940. No particular difference was found in the average extent of disease being treated in the two periods. The incidence of sputum-"positive" cases was higher in the later group. This may be explained, however, by the introduction of sputum and gastric cultures at about this time. The only detectable change in the treatment given was a significant prolongation of "modified" bed rest.

The most likely explanation of this phenomenon is believed to be an increase in the incidence of *newly acquired tuberculosis*[3] in patients admitted in 1936 to 1940. This conclusion was supported by two additional observations: (*1*) 35 of the 41 *proved* cases of newly acquired disease were admitted in 1936 to 1940; (*2*) the incidence of lesions classified as of "recent" onset on the basis of history and character of roentgenographic shadows (figure 3) was 48 per cent in the 1930 to 1935 group, and 56 per cent in the 1936 to 1940 group, a probably significant difference; and finally, 19 per cent of the 1930 to 1935 cases were classified as "old," and only 9 per cent were so classified in the 1936 to 1940 group.

Furthermore, it seems quite possible that a subtle change in the type of case being admitted in the years 1936 to 1940 may be explained by the awakened interest in tuberculin surveys and in routine and mass roentgenography which took place in the mid nineteen thirties (29). A much more conservative attitude toward the handling of so-called "latent" newly acquired tuberculosis was also noted (14, 30).

Much stress is now being placed upon the instability and potential hazards of the newly acquired lesion (3, 8, 23). The "early" lesion appearing soon after

[3] In this report *newly acquired tuberculosis* is defined as a tuberculous pulmonary lesion which develops within a year after a negative chest film. Recent tuberculin conversion is not mandatory (8).

tuberculin conversion is reported to be particularly hazardous (14, 31), although some observers (6, 32, 33) do not agree. Chaves (34) has recently reported a series of 22 persons over 40 years of age with newly acquired lesions which showed a remarkable tendency to progress, in spite of the presumed protection of the age of the patients.

The findings of this study tend to support the opinion (2, 14) that newly acquired disease is potentially serious insofar as danger of reactivation is concerned. They also suggest that there may be a difference in prognosis between the minimal lesion of a year's duration or more and the newly acquired minimal lesion.

Quite in accord with Lurie's findings in animals regarding the inherent constitutional factor, it appears very likely that a group of patients with newly acquired minimal disease is composed of a mixture of three types of cases: (a) those who will do well with or without treatment; (b) those who will do well only with treatment and often after a prolonged period of clinical instability; and (c) a few who will never do well or who will do poorly for varying lengths of time *in spite of* good treatment. A wide variation in the proportion of these three types of patients in any series of newly acquired or minimal lesions may explain the wide disagreement (3, 4, 14, 18) regarding the need and type of treatment indicated for minimal disease, particularly when the patient is asymptomatic.

Any group of minimal tuberculosis cases will reveal many undated lesions, an undetermined percentage of which are of several years' duration. It appears logical, as a result of these observations, that the higher the incidence of such older lesions in a series, the better will be the prognosis for the group studied. In other words, patients whose disease does not progress beyond the minimal stage for a year or more without treatment have already demonstrated an appreciable degree of natural or acquired immunity. Immunity to tuberculosis in patients with a newly acquired minimal lesion, on the other hand, is unproved at the outset. An unknown percentage of such cases will progress to moderately or far advanced disease, often within a few months or even weeks.

This study unfortunately does not settle the question of the correct treatment for minimal tuberculosis. It does, however, provide a means of comparison of "modified" bed rest with other forms of treatment.

The whole subject of the type and duration of bed rest in pulmonary tuberculosis is still in great need of clarification. How much does "strict" bed rest differ from the less stringent regimen of "modified" bed rest as it is actually applied in the average sanatorium? Is it more important that the patient remain within the confines of a bed, or that he spend most of his time in a relaxed and, more particularly, horizontal position? Does the type or the duration of bed rest play the more important part in the healing of pulmonary tuberculosis? Does the use of the bedpan produce less stress and harmful effect on the lungs than a short walk to and from the bathroom? It is the writers' opinion that in actual practice "modified" bed rest may actually result in as much rest of the lungs per 24-hour period as some so-called "strict" bed rest regimens.

Attention, therefore, again (2) is directed to the differences of opinion, the lack of clear-cut definition of terms, the fundamental lack of physiologic knowledge

about how bed rest produces its unquestioned beneficial effects, and the lack of any controlled studies permitting a valid comparison of the various regimens of rest. It is hoped that the limited evidence presented herein may stimulate the reporting of results obtained with "strict" bed rest and other regimens in comparable series of patients.

SUMMARY AND CONCLUSIONS

1. There were 577 patients classified as having "minimal" pulmonary tuberculosis on admission to Trudeau Sanatorium in the eleven years from 1930 through 1940. In retrospect, 307 of these patients were determined to have had *uncomplicated active* minimal pulmonary tuberculosis, 289 of whom were followed for seven years or more after discharge and were subjected to a statistical analysis.

2. After initial treatment with "modified" bed rest, the cumulative incidence of one reactivation or more during the period of treatment and for seven years following discharge was 37 per cent.

3. The late results of "modified" bed rest treatment were favorable: only 3 per cent of the patients had died of tuberculosis, and 4 per cent were chronically ill with the disease in 1948 to 1949. Except for those dead from nontuberculous causes, the balance were well and working when last contacted.

4. There was a significant relationship between the incidence of reactivation and the following: the age of females, the estimated age of the lesion, the extent of involvement, the presence of symptoms, the time spent in the sanatorium, and the time spent away from full employment.

5. There was no significant relationship between the incidence of reactivation and the following: the age of males, constitutional symptoms, the location of the lesion, one or more "positive" versus "negative" sputum findings, the rapidity and degree of clearing on serial roentgenograms, the presence of rales or elevated sedimentation rate on admission, and the duration of "modified" bed rest.

6. Evidence is presented suggesting that the newly acquired minimal lesion is potentially more hazardous than the older minimal lesion.

7. There is need for controlled and comparative studies to assess the relative merits of "modified" bed rest, more lenient regimens, and the "strict" rest regimens used in the treatment of minimal pulmonary tuberculosis.

SUMARIO Y CONCLUSIONES

Resultados del Tratamiento de la Tuberculosis Pulmonar Mínima Activa con el Encamamiento "Modificado": Análisis Estadístico de 289 Enfermos Observados durante Siete Años después de darlos de Alta del Sanatorio Trudeau

1. En los once años transcurridos desde 1930 hasta 1940 inclusive, 577 enfermos fueron clasificados como casos de tuberculosis pulmonar "mínima" a su ingreso en el Sanatorio Trudeau. Considerados retrospectivamente, en 307 se determinó que tenían tuberculosis pulmonar mínima *activa no complicada*, y 289 de ellos fueron observados por espacio de siete años o más después de darlos de alta, siendo objeto de un análisis estadístico.

2. Después del tratamiento inicial con el reposo en cama "modificado", la incidencia acumulativa de una reactivación o más durante el período de tratamiento y los siete años consecutivos al alta representó 37 por ciento.

3. Los resultados tardíos del encamamiento terapéutico "modificado" fueron favorables: sólo 3 por ciento habían fallecido de tuberculosis y 4 por ciento estuvieron crónicamente enfermos con la dolencia en 1948–49. Aparte de los fallecidos de causas no tuberculosas, los demás se hallaban bien y trabajando al ser interrogados por última vez.

4. Hubo una relación significativa entre la incidencia de reactivación y los siguientes factores: edad de las mujeres, edad calculada de la lesión, extensión de la invasión, presencia de síntomas, tiempo pasado en el sanatorio y tiempo pasado sin trabajar plenamente.

5. *No* hubo relación significativa entre la incidencia de reactivación y los siguientes factores: edad de los varones, síntomas constitucionales, situación de la lesión, uno o más hallazgos de esputos positivos en contraposición a negativos, rapidez y grado del despejo en las radiografías seriadas, presencia de estertores o elevación de la eritrosedimentación al ingreso y duración del descanso en cama "modificado."

6. Los datos presentados inidican que una lesión mínima recién adquirida es potencialmente más peligrosa que que una mínima antigua.

7. Necesítanse estudios comprobados y comparados para justipreciar los relativos méritos del descanso en cama "modificado," los régimenes menos rígidos y los régimenes de descanso "estricto" usados en el tratamiento de la tuberculosis pulmonar mínima.

Acknowledgment

The statistical analyses for significance were carried out by Mrs. Ruth Snider, Trudeau, New York, formerly of Toronto, Ontario, to whom the authors are indebted.

REFERENCES

(1) Edwards, H. R.: Tuberculosis case finding: Studies in mass surveys, Am. Rev. Tuberc., 1940, Supplement to vol. *41*.

(2) Anderson, R. S.: Changing concepts in the bed rest treatment of tuberculosis, Dis. of Chest, 1948, *14*, 167.

(3) Amberson, J. B., Jr.: Management of minimal tuberculosis (Editorial), Am. Rev. Tuberc., 1947, *56*, 62.

(4) Hilleboe, H. E., and Holm, J.: Guide for disposition of persons with abnormal pulmonary findings on X-ray films, Pub. Health Rep., 1946, *61*, 1759.

(5) Hilleboe, H. E.: What is early tuberculosis? Pub. Health Rep., 1946, *61*, 1295.

(6) Hilleboe, H. E.: Economy of bed usage in tuberculosis, Pub. Health Rep., 1947, *62*, 185.

(7) Weber, F. J.: The community as a force in the control of tuberculosis, Pub. Health Rep., 1947, *62*, 1283.

(8) Childress, W. G.: Clinical evaluation, treatment and follow-up of newly acquired tuberculous lesions, N. Y. State J. Med., 1947, *47*, 2560.

(9) Bobrowitz, I. D., Hurst, A., and Martin, M.: Minimal tuberculosis: The prognosis and clinical significance of a sanatorium treated group, Am. Rev. Tuberc., 1947, *56*, 110.

(10) KRUGER, A. L., POTTER, B. P., AND JAFFIN, A. E.: Management of the minimal tuberculous lesion, Am. Rev. Tuberc., 1942, *46*, 50.
(11) PECK, W. M., AND WILLIS, H. S.: The modalities of bed rest, Pub. Health Rep., 1946, *61*, 626.
(12) PRATT, J. H.: The importance of prolonged bed rest in the treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1918, *1*, 637.
(13) PRATT, J. H.: The evolution of the rest treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1944, *50*, 185.
(14) AMBERSON, J. B., JR.: The lasting cure of early pulmonary tuberculosis, J. A. M. A., 1937, *109*, 1949.
(15) COHEN, R.: Functional rest cure, Rev. de la tuberc., 1947, *11*, 674.
(16) BROWN, L., AND HEISE, F. H.: The effect of six weeks' bed rest upon patients entering Trudeau Sanatorium, Am. Rev. Tuberc., 1922, *6*, 926.
(17) BROWN, L.: The present status of the treatment of pulmonary tuberculosis, Ann. Int. Med., 1936, *10*, 147.
(18) BRAY, H. A.: Strict bed rest in pulmonary tuberculosis: An appraisal, Am. Rev. Tuberc., 1945, *52*, 483.
(19) HILL, B.: Principles of Medical Statistics, London, Lancet, Ltd., 1939.
(20) CHANG, R.: Minimal pulmonary tuberculosis, Am. Rev. Tuberc., 1948, *58*, 612.
(21) REISNER, D., AND DOWNES, J.: Minimal tuberculous lesions of the lung: Their clinical significance, Am. Rev. Tuberc., 1945, *51*, 393.
(22) ROPER, W. H.: Unpublished data.
(23) REISNER, D.: Incipiency and evolution of pulmonary tuberculosis: II. Behaviour of the initial lesion and course of the disease during observation period, Am. Rev. Tuberc., 1948, *57*, 229.
(24) ORREGO-PUELMA, H., AND GREBE, G.: Analysis of 100 cases of minimal pulmonary tuberculosis, Dis. of Chest, 1945, *11*, 375.
(25) HELLER, R.: The treatment of minimal tuberculous chest lesions, Tubercle, 1947, *28*, 49.
(26) STEPHENS, M. G.: Follow-up of 1,041 tuberculous patients, Am. Rev. Tuberc., 1941, *44*, 451.
(27) WHERRETT, G. J.: Follow-up information on 2,031 tuberculosis patients one to thirteen years after discharge from sanatoria, Am. Rev. Tuberc., 1935, *31*, 62.
(28) BOBROWITZ, I. D.: Prognosis and treatment of minimal tuberculosis, Am. Rev. Tuberc., 1942, *45*, 144.
(29) SOPER, W. B., AND AMBERSON, J. B., JR.: Pulmonary tuberculosis in young adults, particularly among medical students and nurses, Am. Rev. Tuberc., 1939, *39*, 9.
(30) HETHERINGTON, H. W., MCPHEDRON, F. M., LANDIS, H. R. M., AND OPIE, E. L.: Further study of tuberculosis among medical and other university students, Arch. Int. Med., 1935, *55*, 709.
(31) ALT, H. L., BARTH, E. E., AND DAY, A. A.: Tuberculosis in medical students, Am. Rev. Tuberc., 1941, *44*, 346.
(32) MYERS, J. A., CH'IU, P. T. Y., AND STREUKENS, T. L., JR.: Primary infection in adults: Its clinical and epidemiological aspects, Am. Rev. Tuberc., 1939, *39*, 232.
(33) BADGER, T. L., AND AYVAZIAN, L. F.: Tuberculosis in nurses: Clinical observations on its pathogenesis as seen in a 15-year follow-up of 745 nurses, Am. Rev. Tuberc., 1949, *60*, 305.
(34) CHAVES, A. P.: Incipient pulmonary tuberculosis in persons over forty, Am. Rev. Tuberc., 1949, *59*, 469.

INCIDENCE AND SIGNIFICANCE OF THROMBOEMBOLISM IN PULMONARY TUBERCULOSIS[1]

RUSSELL S. JONES,[2] THOMAS C. BLACK,[3] AND HAROLD A. SPARR

(Received for publication November 4, 1949)

INTRODUCTION

In recent years the pathogenesis of pulmonary thromboembolism has been extensively investigated. However, there has been no effective demonstration of the incidence and significance of thromboembolism in pulmonary tuberculosis, although the rarity of pulmonary infarction in tuberculosis has been emphasized. Fox and collaborators (1) in 1948 reiterated Coryllos' (2) report of 1935 that pulmonary infarction is infrequent in tuberculosis. Fox states that pulmonary infarction was observed in only 22 of the 2,182 autopsies on tuberculosis patients. Similar observations have been made by Peck and Willis (3) and by Zins (4). It is regrettable that these investigators were concerned with pulmonary infarcts only and made no reference to the incidence of pulmonary thromboembolism unaccompanied by infarction. A recent study by Zahn and Pierce (5) was specifically related to pulmonary thromboembolism and venous thrombosis in tuberculosis. In a review of the protocols of 1,700 necropsies on tuberculous patients, they found that only 2.1 per cent had pulmonary thromboembolism and/or peripheral venous thrombosis. By excluding the thromboembolism cases which had recent surgery or congestive heart failure, they arrived at a "corrected" figure of 1.5 per cent.

It is the purpose of this paper to indicate: (*1*) greater frequency of pulmonary thrombotic emboli in pulmonary tuberculosis than is generally believed; (*2*) importance of small emboli lodging in the arteries of the good pulmonary tissue in cases of marked pulmonary tuberculosis; (*3*) rarity of infarction associated with these emboli.

METHODS AND MATERIALS

Sixty autopsies were performed upon patients who died with pulmonary tuberculosis at the Lamar Avenue Veterans Hospital. In 25 of the cases a routine autopsy was performed but in the last 35 cases a very careful examination of the lungs was conducted. Both lungs were removed together and, while still attached to the trachea and with intact pleura, they were reinflated by 10 per cent formalin under low gravity pressure. After one week's fixation the lungs were serially sectioned. The parallel planes of sectioning were along the apicobasilar axis and

[1] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[2] University of Tennessee College of Medicine, Department of Pathology.

[3] Present address: Orlando, Florida.

perpendicular to the mediastinum. The sections thus made were comparable to postero-anterior roentgenograms. This method was originally devised for a separate study on the correlation of roentgenographic and pathologic findings. The method of Belt (6) would probably be superior to the above method for detection of many pulmonary emboli. Routine microscopic studies of the lungs and other viscera and of the emboli were done. Examination of the veins of the lower extremities was not permitted.

OBSERVATIONS

Eleven examples of pulmonary thromboembolization were found on careful post-mortem examination of 60 consecutive tuberculous male patients with an incidence of 18.33 per cent. In only one case were the pulmonary emboli associated with infarction. This is comparable to previous reports for pulmonary infarction in pulmonary tuberculosis (1, 3). None of these cases showed any significant cardiac disease such as hypertension, left ventricular hypertrophy, myocardial fibrosis, valvular alterations, or marked coronary arteriosclerosis. There was no chronic passive congestion of the lungs.

Three of the 11 cases of thromboembolization showed moderate, and 2 showed mild, right ventricular hypertrophy[4]. Congestive failure occurred in only one of these. Two of the 11 patients died suddenly and a diagnosis of pulmonary embolism or coronary infarction was suspected because of the clinical picture of cyanosis, dyspnea, sudden severe precordial pain, and prostration. The other 9 patients had relatively mild symptoms which could have been produced by thromboembolization. At the time, however, these symptoms were believed to be caused by the marked underlying pulmonary disease.

Nine of the 11 patients, or approximately 82 per cent, were over 40 years of age. This age distribution for pulmonary thromboembolism is similar to that reported by others.

In the two weeks preceding death from tuberculosis, a reduction in the fluid intake frequently occurs because of the patient's serious illness. In order to avoid excessive hemoconcentration developing in these patients, attempts were made to provide adequate fluids during this period except when contraindicated.

DISCUSSION

Pathogenesis of pulmonary thromboemboli: The sites of venous thrombosis have been thoroughly studied (7, 8, 9). Any portion of the systemic venous circulation and right heart may be the source of pulmonary emboli. Some studies have emphasized the right heart (10), some the periprostatic and pelvic veins (11); but most have stressed the significance of the veins of the lower extremities and especially of the calves (7, 12, 13).

The thrombosis of systemic veins unassociated with any infiltrative or inflam-

[4] The evaluation of the weights of the cardiac chambers, and specifically of the right ventricle, is based upon a study of 500 autopsies by one of us (R. S. J.). The details and conclusions will be published at an early date.

matory process has been related to many factors. These factors may be classified as follows:

I. Reduced venous blood flow (stasis) (14)
   (a) Local pressure (pillows under popliteal fossa (12), crossings of tendons and ligaments (7, 8), abdominal binders (15), Fowler's position (15))
   (b) Lack of movement (bed rest, surgery (16, 17), hypnotics and analgesics (18))
   (c) Congestive heart failure (10, 11, 19, 20)
   (d) Immobile diaphragm (21, 22)
   (e) Reduced peripheral arterial blood flow (arteriosclerosis, cold weather, smoking, vasospasm (16))

II. Alterations in circulating blood
   (a) Increased blood viscosity
      (*1*) Hemoconcentration (bed rest (23), shock, burns, dehydration, polycythemia
      (*2*) Increased plasma viscosity (hyperglobulinemia (24), local increase in carbon dioxide)
   (b) Increased cold agglutinins (25) and cryoglobulins
   (c) Increased calcium (24)
   (d) Increased platelets (26) and platelet agglutinability (27) (postoperative, puerperal)
   (e) Hyperprothrombinemia (28)
   (f) Increased protein catabolism (24)

III. Alteration in venous walls
   (a) Endothelial injury (from muscle products (8), collapsed vein walls (13), anoxemia)
   (b) Local trauma

IV. Age (29, 30, 31) (This may be related to any of the above factors or possibly to reduced heparin from a decreased number of mast cells (32) because of age.)

The question of relationship of blood volume to thrombosis has been neglected and deserves investigation. Unfortunately no blood volume determinations were made on our cases. One would have expected, however, a reduced blood volume to be present in our chronically ill and debilitated patients (33, 34). The concept of a reduced blood volume in such patients may be fallacious since it is based upon the usual or former weight rather than upon the actual weight. Debilitated and hypoproteinemic patients apparently tolerate surgical procedures (34)much better after increasing the blood volume, erythrocytes, and hemoglobin by multiple blood transfusions prior to surgery. The idea of "chronic shock" and the calculation of blood volume upon the former, rather than actual, body weight helps to explain this improved response to surgery. The multiple blood transfusions in chronically ill patients may also improve protein regeneration and may increase the tissue fluids.

It is conceivable that a debilitated patient with a reduced blood volume would have the same capillary bed which the patient had when well nourished, although these capillaries would contain less blood or more capillaries would be collapsed. In surgical procedures and anesthesia this potentially greater capillary bed may become refilled, giving rise to the syndrome of shock and peripheral vascular collapse. It is possible that by some related mechanism a reduced blood volume might lead to stasis and thence to thrombosis. Bed rest (23) alone produces a re-

duced blood volume but this is apparently related to a plasma decrease and not to the erythrocyte and hemoglobin deficiency of debilitation.

The theoretically reduced blood volume in our patients seems opposed to the condition in which pulmonary thromboembolism is most frequent, i.e., congestive heart failure with increased blood volume. The 18.33 per cent incidence of pulmonary thromboembolism in our cases is not as great as in congestive heart failure since Belt (35) reported an incidence of about 30 per cent pulmonary thromboembolism and White (20) reported an incidence of 30 per cent pulmonary infarction in this condition. The 18.33 per cent incidence of thromboembolism in the present series is somewhat higher than the incidence of thromboembolism in any large series of unselected cases. Hunter (12) found an incidence of 14.6 per cent; DeTakat (36), 10 per cent; and Lubarsch (as quoted by Møller (37)) reported an incidence of 18 per cent. In the cases of the present study peripheral venous congestion cannot be excluded as a factor in thromboembolism since 5 patients had moderate right-ventricle hypertrophy. Only the patient with the most marked hypertrophy had congestive failure. Four of the 11 cases showed mural thrombi in the right ventricle, and the case with the pulmonary infarct had mural thrombi in the left ventricle as well.

Thromboembolism and pulmonary infarction: Only one of the 11 cases of pulmonary thromboembolization was accompanied by infarction. Belt (35) estimates that about 30 per cent of pulmonary emboli are associated with infarction in unselected autopsies. The incidence of one pulmonary infarction in a total of 60 autopsies on tuberculous patients in the present study is similar to the previously mentioned observation of Fox (1) in patients dying with tuberculosis. The significance of passive pulmonary congestion in pulmonary infarction is suggested by the cases of Spain and Moses (38). Of their 100 cases of pulmonary infarction, 82 had heart disease. White (20) reported an incidence of pulmonary infarction in 30 per cent of the cardiac patients. Karsner (39) in 1912 emphasized that obstruction of the venous flow from the lung was the prerequisite for experimental pulmonary infarction.

The dual blood supply of the pulmonary and bronchial arteries plus the intralobar pulmonary anastomoses prevent the necrosis of tissue upon occlusion of the pulmonary arteries. Bronchial and pulmonary arterial flow is altered, not only by obstructed pulmonary veins, but apparently by compression of the capillary bed of the lung as from edema (40) and intrathoracic masses. The efficient function, but not the survival, of pulmonary tissue depends upon the intact pulmonary arterial flow.

While the bronchial arterial supply is increased to the involved areas (41) in tuberculosis, it is questionable that it is the most significant factor in preventing infarction in pulmonary thrombotic embolization. The lack of edema or congestion may be more important. In the present cases of thromboembolization only one pulmonary infarct was present. This patient had mural thrombi in the left as well as in the right ventricle, but no pre-embolic passive pulmonary congestion could be detected. The other patients presented no evidence of left ventricular failure or pulmonary congestion.

There are few reports which indicate the site of lodgment of emboli in the pulmonary arteries although the sites of pulmonary infarction have been well described. Evoy (9) found 42.3 per cent of pulmonary infarcts in the right lower lobe and 38.4 per cent in the left lower lobe. In Zins' (4) cases approximately 50 per cent occurred in the right lower lobe and 25 per cent in the left lower lobe. It is obvious that most infarcts occur in the lower lobes. The reasons for this are unknown; but the relative caliber of the arteries, the relative venous pressures, and stasis have been suggested.

Location of thrombotic emboli in pulmonary tuberculosis: In most of the present cases, as indicated by the illustrations (figure 1), the emboli lodged in the pulmonary arteries supplying the tissue least involved by tuberculosis. In some of the cases there was only one relatively uninvolved lobe and the main vessel to this lobe was the one which was occluded by the thrombotic embolus. Three of the 11 patients with pulmonary embolism also had thromboses of some of the pulmonary arteries but these were readily distinguished from the emboli and occurred adjacent to, or near, the areas of most marked tuberculous involvement.

As an explanation for the lodgment of pulmonary emboli in the vessels to the remaining good lung, two possible influences are suggested: (*1*) the location in the lower lobes which are the most frequent sites of emboli and least frequent site of tuberculosis, (*2*) the increased blood flow through the remaining uninvolved lung in marked pulmonary tuberculosis.

In the areas of extensive pulmonary tuberculosis, the accompanying pulmonary arterial changes (41) and reduced function of the diseased tissue leave the burden of aeration of blood to the remaining good pulmonary tissue. When significant portions of the pulmonary arterial bed are obstructed by the disease process, the vessels of the remaining uninvolved tissue readily accommodate the arterial flow (43). In some of the cases of the present study, however, the disease was sufficiently marked to result in a hypertrophy of the right ventricular myocardium, suggesting that intrapulmonary vascular resistance and pulmonary arterial pressure were increased. Assuming there was no marked reduction in the minute-volume, the uninvolved lung must have accommodated an increased blood flow through its vessels.

Important factors in the pathogenesis of pulmonary thrombeombolism in tuberculosis: The incidence of pulmonary thromboembolism in the present series is so sharply different from that of other studies on patients dying of tuberculosis that some explanation is sought. The different techniques of examining the lung may be one explanation. Most of the cases were carefully examined by serial sections of the lungs, while other reports have been based upon the review of autopsy protocols. The prosector's interest in the pulmonary tuberculosis might lead him to overlook the smaller emboli which nevertheless might serve as the fatal episode. Furthermore, in tuberculosis there are very few infarcts which would immediately lead the prosector to search for emboli; and if pulmonary emboli are not observed one does not generally examine the leg veins in routine autopsies. Thus, a low incidence of both pulmonary thromboembolism and peripheral venous thrombosis might be obtained in pulmonary tuberculosis.

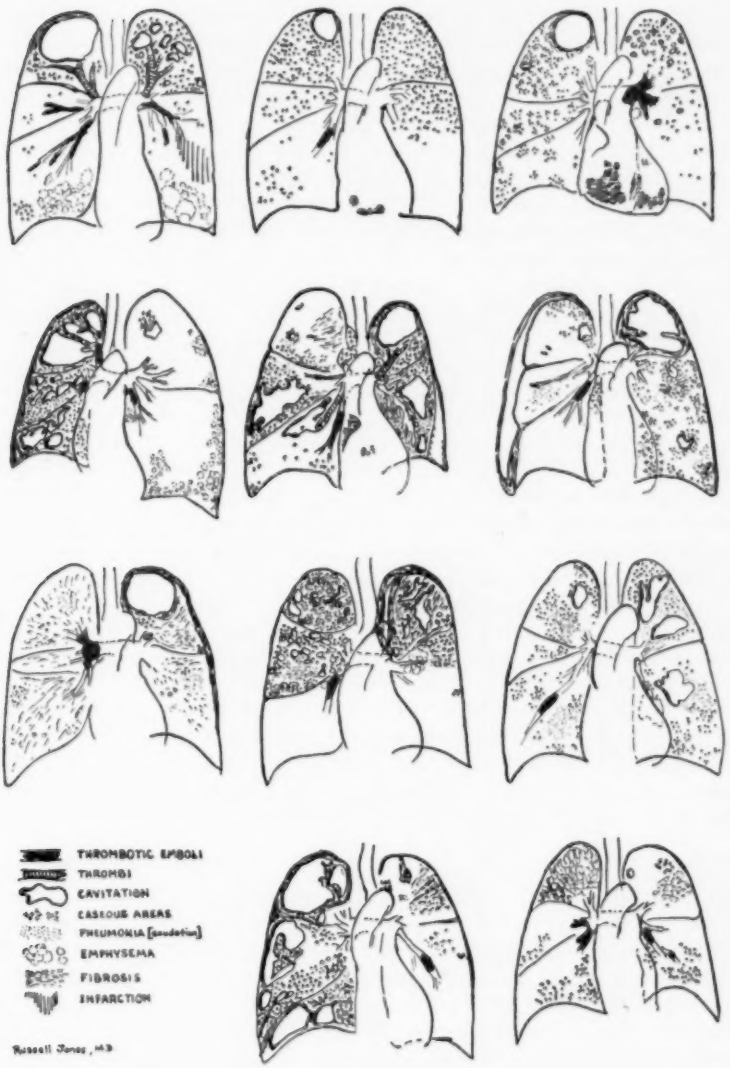


FIG. 1. The semidiagrammatic illustrations of the cases of pulmonary thromboembolism indicate: (*1*) The emboli are in the arteries supplying the pulmonary tissue showing the least tuberculous involvement; (*2*) infarction is present in only one case; (*3*) thromboses of the pulmonary arteries are near areas of greatest tuberculous involvement.

The role of stasis appears important. The marked pulmonary tuberculosis was accompanied by cor pulmonale in 5 of the 11 cases (45.5 per cent) but mild cor pulmonale was also present in 20 per cent of the remaining 49 cases without pulmonary embolism. Mural thrombi in the right ventricle and auricle were common in the thromboembolism cases, however, as contrasted with the cases without this complication. No information on cor pulmonale is available from previous studies on tuberculosis and pulmonary embolism or pulmonary infarction. A reduced blood volume might be a factor, but information on this is so meager that evaluation must await further data. Dehydration and hemoconcentration may be significant. Zahn and Pierce's (5) comparatively low incidence of venous thrombosis and thromboembolism in tuberculosis may be due to the good hydration of their patients, since they state that their patients received more fluids than nontuberculous individuals.

The older literature on thrombophlebitis (44, 45, 46) in tuberculosis indicates the association of these two processes ranging from Gray's 0.5 per cent to Lubarsch's (quoted by Buckley (4)) 14 per cent. Again this may have been due to dehydration but there are so many other factors already outlined which also might be explanations that further investigations on patients before, as well as after, death must be carried out before the subject is clarified. Age may be used to emphasize the interrelation of many of the factors outlined above. Why most pulmonary emboli occur in patients over 40 years is still unknown but, even in the present tuberculous patients, 9 of the 11 were over 40 years, which is considerably higher than in the nonembolic group.

Significance of pulmonary thromboembolism in tuberculosis: The thrombotic emboli in marked pulmonary tuberculosis not only tend to occlude the pulmonary arteries of the good pulmonary tissue but as a result can produce death by the occlusion of a single lobar artery. The mechanism of death would appear to be the mechanical occlusion of blood flow through the pulmonary arteries (47). This aggravation of a decreased cardiac output and decreased aeration of blood superimposed upon marked pulmonary tuberculosis bring about an abrupt death in patients with an already hopeless prognosis.

SUMMARY

In patients hopelessly ill with tuberculosis, pulmonary thromboembolism may produce the terminal episode. Eleven instances of thromboembolism were found in 60 consecutive post-mortem examinations of patients with marked pulmonary tuberculosis. The emboli in these patients lodged in the arteries supplying the good pulmonary tissues and away from the areas of the main tuberculous involvement. The rarity of infarction in tuberculous patients is discussed.

The high incidence of pulmonary thromboembolism in this series is attributed to: (a) the careful dissection of the lung rather than a review of protocols; (b) the extensive pulmonary tuberculosis with cor pulmonale in 5 of the 11 cases; (c) inadequate fluid intake in seriously ill patients; and (d) age over 40 years in 9 of the 11 cases.

Other factors in venous thrombosis are outlined and the possible relationship of reduced blood volume in chronically ill patients is discussed.

SUMARIO

Incidencia y Significación del Tromboembolismo en la Tuberculosis Pulmonar

En los tuberculosos desahuciados, una tromboembolia pulmonar puede desatar el episodio final. Entre 60 autopsias consecutivas en enfermos con pronunciada tuberculosis pulmonar, descubriéronse 11 casos de tromboembola. Los émbolos en esos casos se alojaban en las arterias que regaban los tejidos pulmonares indemnes, estando alejados de las zonas principalmente afectadas por la tuberculosis. Menciónase la rareza del infarto en los tuberculosos.

Impútase la alta incidencia del tromboembolismo pulmonar en esta serie a: a) la cuidadosa disección del pulmón en vez de mero repaso de los protocolos; b) avanzada tuberculosis pulmonar con cor pulmonale en 5 de los 11 casos; inadecuada ingestión de líquido en los enfermos muy graves; y d) edad de más de 40 años en 9 de los 11 casos.

Señálanse otros factores en la trombosis venosa y la posible relación de la reducción del volumen sanguíneo en los casos crónicos.

REFERENCES

(1) Fox, T. T., Robitzek, E. H., Bernstein, I., and Bobb, A. L.: Bed rest in thromboembolization in tuberculosis, Am. Rev. Tuberc., 1948, *57*, 485.
(2) Coryllos, P. N.: Case Reports, Quart. Bull., Sea View Hosp., 1935, *1*, 131.
(3) Peck, W. M., and Willis, H. S.: Bed rest in tuberculosis: Its dangers and proprieties, Am. Rev. Tuberc., 1945, *52*, 15.
(4) Zins, E. I.: Concerning the location of pulmonary infarction, Am. Rev. Tuberc., 1949, *60*, 206.
(5) Zahn, D. W. and Pierce, C. T.: Venous thrombosis and pulmonary embolism in tuberculosis, Am. J. Med., 1948, *5*, 716.
(6) Belt, T. H.: Demonstration of small pulmonary emboli at autopsy, J. Tech. Methods, 1936, *15*, 39.
(7) Neuman, R.: Ursprungszentren und Entwicklungsformen der Bein-Thrombose, Virchows Arch. f. path. Anat., 1938, *301*, 708.
(8) Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, Virchows Arch. f. path. Anat., 1937, *300*, 180.
(9) Evoy, M. H.: Fatal pulmonary embolism, Northwest Med., 1949, *48*, 114.
(10) Garvin, C. F.: Mural thrombi in the heart as a source of emboli, Am. J. M. Sc., 1941, *201*, 412.
(11) Moran, T. J.: Pulmonary embolism in nonsurgical patients with prostatic thrombosis, Am. J. Clin. Path., 1947, *17*, 205.
(12) Hunter, W. C., Sneeden, V. D., Robertson, T. D., Snyder, G. A. C.: Thrombosis of deep veins of the leg, Arch. Int. Med., 1941, *68*, 1.
(13) Frykholm, R.: The pathogenesis and mechanical prophylaxis of venous thrombosis, Surg., Gynec. & Obst., 1940, *71*, 307.
(14) Rowntree, L. G., Shionoya, T., Johnson, W.: Experimental extracorporeal thrombosis, Tr. A. Am. Physicians, 1927, *42*, 73.
(15) Prows, H. S.: Thromboembolism, Ann. West. Med. & Surg., 1949, *3*, 12.
(16) Smith, L. A., and Allen, E. V.: Circulation time from foot to carotid sinus and from arm to carotid sinus of man, Arch. Surg., 1940, *41*, 1377.
(17) Smith, L. A., and Allen, E. V.: Studies on rate of venous blood flow: Vascular clinics XIV, Proc. Staff Meet., Mayo Clin., 1941, *16*, 53.
(18) Dock, W.: The evil sequelae of complete bed rest, J.A.M.A., 1944, *125*, 1083.
(19) Barnes, A. R.: The problem of pulmonary embolism, West J. Surg., 1942, *50*, 551.
(20) White, P., August, S., and Mitchie, C.: Hydrothorax in congestion failure, Am. J. M. Sc., 1947, *214*, 243.

(21) NISSEN, R., AND WUSTMAN, O.: Der Einfluss Pathologischen Zwerchfellstandes auf die Blutströmung in der unteren Hohlvene, Deutsche Ztschr. f. Chir., 1927, *42*, 203.

(22) FRIMANN-DAHL, J.: Diaphragmabewegungen und der Postoperative Venenstrom, Acta chir. Scandinav, 1935, *36*, 1.

(23) TAYLOR, H. L., ERICKSON, L., HENSCHEL, A., AND KEYS, A.: The effect of bed rest on the blood volume of normal young men, Am. J. Physiol., 1945, *144*, 227.

(24) OCHSNER, A., AND DEBAKEY, M.: Significance of phlebothrombosis and thrombophlebitis in orthopedic surgery, J. Bone and Joint Surg., 1941, *23*, 788.

(25) PETERSON, O. L., HAM, T. A., AND FINLAND, M.: Cold agglutinins (autohemagglutinins) in primary atypical pneumonias, Science, 1943, *97*, 167.

(26) POTTS, W. J., AND PEARL, E.: A study of platelet count and the coagulation of plasma and whole blood following operation, Surg., Gynec. & Obst., 1941, *73*, 492.

(27) MOOLTON, S. E., AND VROMAN, L.: The adhesiveness of blood platelets in thromboembolism and hemorrhagic disorders, Am. J. Clin. Path., 1949, *19*, 701.

(28) SHAPIRO, S.: Hyperprothrombinemia, Exper. Med. & Surg., 1944, *2*, 103.

(29) WELCH, C. E., AND FAXON, H. H.: Thrombophlebitis and pulmonary embolism, J. A. M. A., 1941, *117*, 1802.

(30) ALLEN, A. W., LINTON, R. R., DONALDSON, G. A.: Venous thrombosis and pulmonary embolism, J. A. M. A., 1945, *128*, 397.

(31) VEAL, J. R., AND HUSSEY, H. H.: Surgery of deep venous thrombosis of the lower extremity, Surgery, 1945, *17*, 218.

(32) JORPES, J. E.: Origin and physiology of heparin: Specific therapy in thrombosis, Ann. Int. Med., 1947, *27*, 361.

(33) GREGERSON, M. I.: A practical method for determination of blood volume with the dye, T-1824, J. Lab. & Clin. Med., 1944, *29*, 1266.

(34) CLARK, J. H., NELSON, W., LYONS, C., MAYERSON, H. S., AND DECAMP, P.: Chronic shock: The problem of reduced blood volume in the chronically ill patient, Ann. of Surg., 1947, *125*, 618.

(35) BELT, T. H.: Thrombosis and pulmonary embolism, Am. J. Path., 1934, *10*, 129.

(36) DE TAKATS, G., AND JESSER, J. H.: Pulmonary embolism: Suggestions for its diagnosis, prevention and management, J. A. M. A., 1940, *114*, 1415.

(37) MØLLER, P.: Studien uber Embolische und Autochthoma Thromben in der Arteria Pulmonalis, Beitr. Z. path. Anat. u.z. allg. Path., 1922, *71*, 27.

(38) SPAIN, D. M., AND MOSES, J. B.: Thrombosis and embolism of pulmonary vessels with special reference to pulmonary vein thrombosis, Am. J. M. Sc., 1946, *212*, 707.

(39) KARSNER, H. T., AND ASH, J. E.: Studies in infarction: II. Experimental bland infarction, J. Med. Res., 1912–1913, *27*, 205.

(40) CHAPMAN, D. W., GUGLE, L. J., AND WHEELER, P. W.: Experimental pulmonary infarction, Arch. Int. Med., 1949, *83*, 158.

(41) WOOD, D. A., AND MILLER, M.: The role of the dual pulmonary circulation in various pathological conditions of the lungs, J. Thoracic Surg., 1937, *7*, 549.

(42) SAVACOL, J. W., AND CHARR, R.: Thrombosis of pulmonary artery, Am. Rev. Tuberc., 1941, *44*, 42.

(43) JACOBAEUS, H. C., AND BRUCE, T.: Bronchospirometric study on ability of human lungs to substitute for one another, Acta med. Scandinav., 1940, *105*, 193, 211.

(44) BUCKLEY, R. C.: Thrombo-phlebitis as a later complication in pulmonary tuberculosis, U. S. Vet. Bureau Med. Bull., 1928, *4*, 453.

(45) DODWELL, P. R.: Thrombosis of the femoral veins in phthisis, Am. J. M. Sc., 1893, *105*, 641.

(46) GRAY, E. A.: Thrombophlebitis in tuberculosis with autopsy, M. Rec., 1916, *90*, 636.

(47) PILCHER, R.: The role of obstruction in fatal pulmonary embolism, Lancet, 1939, *1*, 1257.

(48) HOLDEN, W. D., SHAW, B. W., CAMERON, D. B., SHEA, P. J., AND DAVIS, J. H., JR.: Experimental pulmonary embolism, Surg., Gynec. & Obst., 1949, *88*, 23.

THE OCCURRENCE OF PULMONARY TUBERCULOSIS FOLLOWING PULMONARY EXCISION FOR NONTUBERCULOUS DISEASES[1,2]

HARRY L. KATZ

(Received for publication January 20, 1950)

Advances in thoracic surgery have greatly extended the indications for resection of lung tissue. Since 1933, when Graham performed the first successful total pneumonectomy for primary carcinoma, progress has been such that pneumonectomies and lobectomies are no longer extraordinary operations. Pulmonary resection includes such procedures as pneumonectomy, lobectomy, and the excision of bronchopulmonary segments.

The immediate and early complications resulting from pulmonary resection have been stressed by Overholt (1), Churchill (2), and Meade and Kay (3). The complications and their management which have commonly merited attention are: atelectasis, hemothorax, empyema, bronchopleural fistula, overdistention of the remaining lung parenchyma, and cardiac aberrations. However, too little emphasis has been placed on the late complications which may ensue from pulmonary resection.

The present report is concerned with 4 patients who underwent pulmonary resection for nontuberculous pulmonary disease and at various intervals following the resection developed acute, caseous-pneumonic or exudative pulmonary tuberculosis. This complication does not in any manner detract from the great value of pulmonary resection as a surgical procedure in the treatment of pulmonary disease, but stresses the significance of thoroughly excluding coexisting tuberculous disease, as well as the necessity for the adoption of a careful and long-term follow-up program for patients subjected to pulmonary resection.

CASE REPORTS

Case 1. A 27-year-old white male was admitted to Halloran VA Hospital on September 28, 1947 with a history of recurring respiratory infections, cough productive of copious sputum, and four pneumonic episodes since 1943 involving the left lung. Chest roentgenogram on September 29, 1947 (figure 1A) showed an infiltrative process in the left supradiaphragmatic area and circular areas suggestive of bronchiectasis. Bronchoscopic examination revealed reddening of the mucosa of the left lower lobe bronchi; considerable tenacious mucoid sputum filled the left lower lobe bronchial tree. Many sputum examinations were negative for acid-fast bacilli. Bronchography on October 15, 1947 (figure 1B) showed advanced saccular and cylindrical bronchiectasis involving the lingula of the left upper lobe and all basal segments of the left lower lobe.

On December 1, 1947 a lobectomy of the left lower lobe and a lingulectomy were performed. Gross and microscopic examination of the resected tissue showed chronic bronchiectasis associated with pulmonary fibrosis and emphysema.

[1] From the Medical Service, Veterans Administration Hospital, Staten Island, New York.

[2] Sponsored by Veterans Administration and published with approval of Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect opinion or policy of Veterans Administration.

The postoperative course was uneventful, and he was discharged on January 5, 1948. A chest roentgenogram prior to discharge from the hospital (figure IC) revealed complete

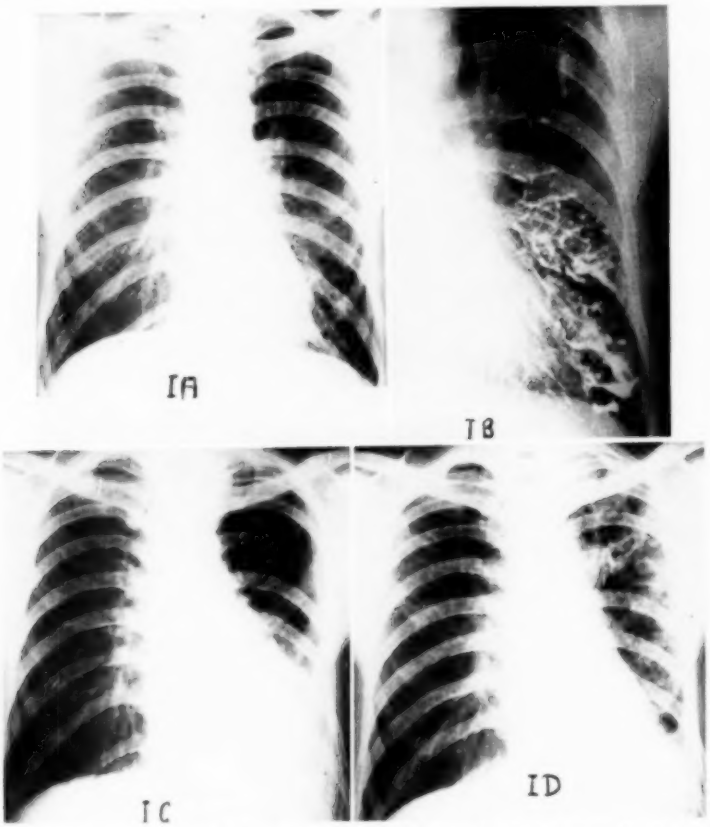


FIG. IA. September 29, 1947. Patchy and fibrotic infiltration in left supradiaphragmatic region; circular areas suggestive of bronchiectatic dilatations are present.

FIG. IB. October 15, 1947. Bronchogram; saccular and cylindrical bronchiectasis involving the lingula of the upper lobe and all basal segments of the left lower lobe.

FIG. IC. December 26, 1947. Postoperative; left upper lobe is expanded to fill the pleural cavity; left diaphragmatic leaf is elevated and the costophrenic angle obliterated by pleural thickening; left distended upper lobe and right lung are free of disease.

FIG. ID. June 2, 1948. Advanced caseous pneumonic and exudative disease involving almost the entire left upper lobe; multiple areas of cavitation are evident.

expansion of the left upper lobe. The diaphragmatic leaf was elevated and the costophrenic angle obliterated by pleural thickening. The right lung as well as the left upper lobe were free of disease.

The patient remained asymptomatic until May 1948 when he was readmitted with com-

plaints of cough, streaking of sputum with blood, left chest pain, weakness, and weight loss. A roentgenogram of the chest on June 2, 1948 (figure ID) showed extensive caseous-pneumonic disease and multiple areas of cavitation in the remaining portion of the left lung. The sputum was positive for acid-fast bacilli. He was treated with bed rest and on September 18, 1948 streptomycin therapy was begun (one Gm. daily for forty-two days). On October 15, 1948 a lobectomy of the left upper lobe was performed, followed one month later by a five-rib thoracoplasty.

The postoperative course was uneventful. Sputum and gastric aspirates became negative for acid-fast bacilli.

Pathologic examination of the left upper lobe showed multiple tuberculous cavities in direct communication with the upper lobe bronchi. The lung parenchyma contained within it many encapsulated caseous and acinous-nodose foci.

Summary: A 27-year-old white male underwent a lingulectomy and left lower lobe lobectomy for bronchiectasis. A roentgenogram at the time of discharge from the hospital showed the remaining lung parenchyma to be free of tuberculous disease. He was readmitted to the hospital five months later with signs, symptoms, and roentgenographic evidence of active and advanced tuberculous disease with cavitation involving the overdistended left upper lobe. Lobectomy of this lobe followed by thoracoplasty resulted in the "conversion" of sputum and complete recovery.

Case 2. A 23-year-old white male had complaints of cough productive of mucopurulent sputum, frequent respiratory infections, and intermittent hemoptyses since 1943, when he had had a pneumonia involving the left lung. Bronchography performed at another hospital in March 1945 revealed extensive bronchiectasis of the left lower lobe, and in April 1945 a left lower lobe lobectomy was done there. However, he continued to have blood-streaked expectoration and episodes of left chest pain associated with fever.

He was admitted to Halloran VA Hospital in January 1948. Seven sputum specimens and gastric aspirates were negative for acid-fast bacilli on concentration and culture. Bronchoscopic examination on January 19, 1948 showed the left lower lobe bronchus to be completely occluded. Bronchography done on March 16, 1948 (figure IIA) revealed residual bronchiectasis in the lingular segment of the left upper lobe. Consequently, a lingulectomy was performed on August 12, 1948. He had an uneventful convalescence, and he was discharged on November 1, 1948. A roentgenogram of the chest at this time (figure IIB) showed basal pleural thickening on the left side. The left upper lobe and right lung were free of disease.

This patient remained well until April 1949 when he began to complain of cough, left chest pain, weight loss, and fever. He was readmitted on May 30, 1949, appearing acutely ill and toxic. A chest roentgenogram on June 2, 1949 (figure IIC) showed extensive caseous-pneumonic disease and multiple large areas of cavitation in the remaining portion of the left upper lobe. The sputum was positive for acid-fast bacilli (Gaffky 8).

Summary: A 23-year-old white male underwent a left lower lobe lobectomy and forty months later a lingulectomy for bronchiectasis. Serial chest roentgenograms during the pre- and post-operative period showed the pulmonary parenchyma to be free of tuberculous disease. He remained essentially asymptomatic until ten months after resection of the lingula, at which time he manifested symptoms and roentgenographic evidence of acute, caseous-pneumonic disease and multiple large areas of cavitation in the remaining overdistended portion of the left upper lobe.

Case 3. A 29-year-old Negro male was admitted to Halloran VA Hospital on August 15, 1947 with complaints of fever of two months' duration, nonproductive cough, and right chest pain. He had been treated at home at various intervals with penicillin and sulfonamides,

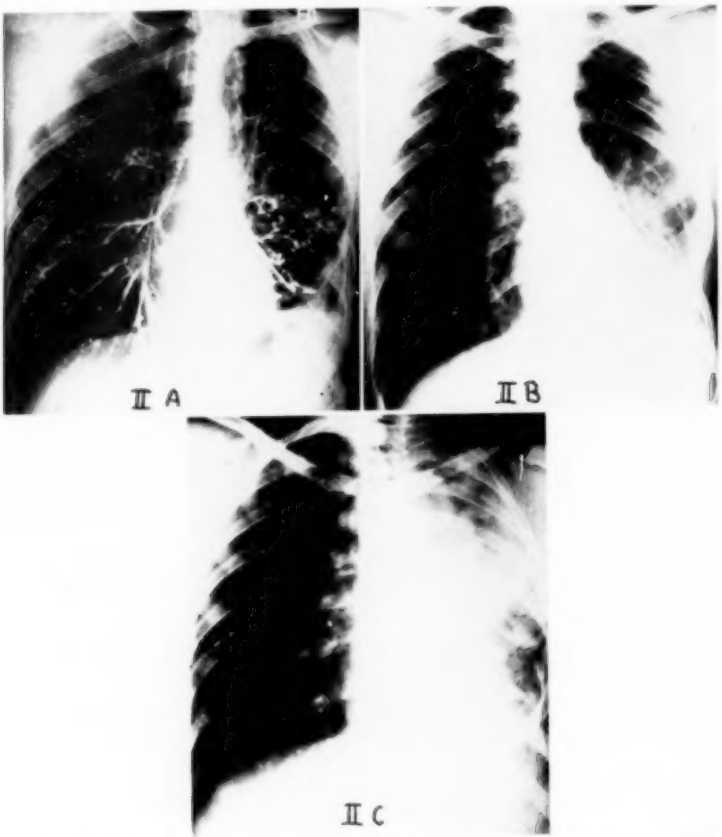


FIG. IIA. March 17, 1948. Bronchogram; residual bronchiectasis in lingular segments of left upper lobe; basal pleural thickening and elevation of diaphragmatic leaf.

FIG. IIB. November 12, 1948. Postlingulectomy; basal pleural thickening and regenerated rib are evident; the right lung and remaining left upper lobe are free of tuberculous disease.

FIG. IIC. June 2, 1949. Extensive caseous pneumonic and exudative disease occupying entire left upper lobe; multiple large areas of cavitation are present.

with only temporary improvement. Examination of the chest showed impaired resonance, bronchovesicular breath sounds, and crepitant rales throughout the base of the right lung.

Eight sputum examinations by concentration and culture were negative for acid-fast bacilli and fungi. Sputum cultures were positive for *Streptococcus viridans* and *Staphylococcus aureus*. A roentgenogram of the chest on August 23, 1947 (figure IIIA) showed an irregular

pneumonic infiltration radiating from the hilar region into the right base. The remainder of the lung fields were clear. A tomographic roentgenogram (figure IIIB) revealed a narrowing of the right lower lobe bronchus. Areas of cavitation were not visualized in either lung. Bronchoscopic examinations revealed a purplish adenomatous mass, 1.0 cm. in diameter, obstructing the basal division of the right lower lobe bronchus just below the level of the dorsal segment.

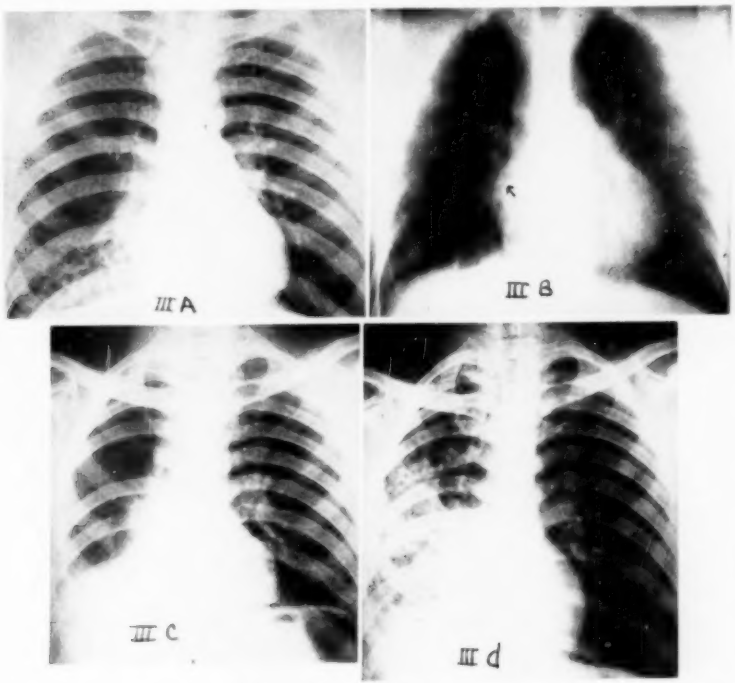


FIG. IIIA. August 23, 1947. Patchy pneumonic infiltration radiating from hilum into right supradiaphragmatic region; remainder of the lung fields are clear.

FIG. IIIB. September 26, 1947. Tomography; bronchial narrowing of the right lower lobe bronchus; cavities are not present in either lung field.

FIG. IIIC. December 8, 1947. Postoperative; basal pleural thickening and elevation of the right diaphragm; right upper lobe and left lung are free of disease.

FIG. IIID. September 29, 1948. Diffuse exudative and caseous pneumonic disease in the lower two-thirds of the overdistended right upper lobe; multiple cavities are present.

On October 9, 1947, an exploratory thoracotomy was performed. Extensive hilar adenopathy was present, and an adenomatous growth was seen in the right lower lobe bronchus just below the middle lobe orifice. Consequently, both the middle and lower lobes were resected. A few hilar nodes were also removed.

The histologic appearance of both the adenomatous tissue and hilar lymph nodes was that of sarcoidosis. The resected right lower lobe contained many small pyogenic abscesses,

bronchopneumonic areas, bronchiectasis, pulmonary emphysema, and fibrosis. There was no gross or microscopic evidence of tuberculous disease in the resected lung tissue.

The postoperative course was uneventful, and the patient was discharged on December 8, 1947. A chest roentgenogram at this time (figure IIIC), showed the remaining lung parenchyma to be free of tuberculous disease. He remained well until September 1948, when he developed fever, cough, right chest pain, and progressive weight loss.

He was readmitted to the hospital on September 28, 1948. His temperature ranged from 101° to 102°F. A roentgenogram of the chest on September 29, 1948 (figure IIID), showed a diffuse exudative and caseous-pneumonic infiltration involving the lower two-thirds of the remaining right upper lobe. Multiple cavities were present within this area. Sputum specimens were positive for acid-fast bacilli (Gaffky 8).

Summary: A 29-year-old Negro male was admitted to the hospital with signs and symptoms of right lower lobe endobronchial disease, manifested by repeated episodes of pneumonitis. Bronchoscopic examination and an exploratory thoracotomy led to the diagnosis of an endobronchial adenoma. However, histologic examination revealed the lesion to be an endobronchial sarcoid granuloma. A right middle and lower lobe lobectomy were performed.

The resected tissue showed no evidence of tuberculous disease. Eleven months after the pulmonary resection this patient developed acute caseous-pneumonic disease, with cavitation in the overdistended right upper lobe.

Case 4. A 51-year-old Negro male was admitted to Halloran VA Hospital on October 18, 1947 with a six months' history of cough productive of copious foul sputum, weakness, and weight loss of about forty pounds. On admission he was critically ill, dehydrated, and dyspneic.

A roentgenogram of the chest on October 20, 1947 (figure IVA) showed a hydropneumothorax on the right, massive consolidation of the lower half of the right lung, and large areas of cavitation in the mid-lung field.

The clinical course and roentgenographic appearance of the disease were consistent with an extensive gangrene of the right lung. Examinations of sputum were consistently negative for acid-fast bacilli, but cultures were positive for *Actinomyces bovis* and nonhemolytic *Streptococci*. Intercostal drainage of the right pleural space was instituted on October 21, 1947. The pleural fluid was purulent, tenacious, foul, and positive on culture for *Actinomyces bovis*.

On January 7, 1948 the right middle and lower lobes were removed. Examination of the resected tissue showed extensive actinomycosis, abscess formation, bronchopneumonic areas in various stages of organization, and suppurative pleuritis.

Postoperatively, the patient developed an empyema which again required drainage. On March 23, 1948, a right upper lobe lobectomy with debridement of the pleural cavity was performed, followed two months later by decortication of the empyema space and thoracoplasty. However, a residual small empyema pocket remained. On November 5, 1948 this pocket was unroofed and filled with a pedicle flap of muscle, and primary closure was accomplished.

The patient's condition improved progressively, he became afebrile, and gained thirty pounds in weight. He was discharged on November 24, 1948. A chest roentgenogram at this time (figure IVB) showed the evidence of right pneumonectomy and complete thoracoplasty. The left lung was free of disease.

He returned to the hospital on July 29, 1949 because of increasing dyspnea, cough, and weight loss. A roentgenogram of the chest on August 2, 1949 (figure IVC) showed an infiltrative process radiating from the left hilar region into the first and second intercostal spaces anteriorly. Small areas of rarefaction were present within this density. Specimens of sputum were positive for acid fast bacilli.

Summary: A 51-year-old Negro male was hospitalized with signs and symptoms of acute suppuration of the right lung and pleural space caused by *Actinomyces*

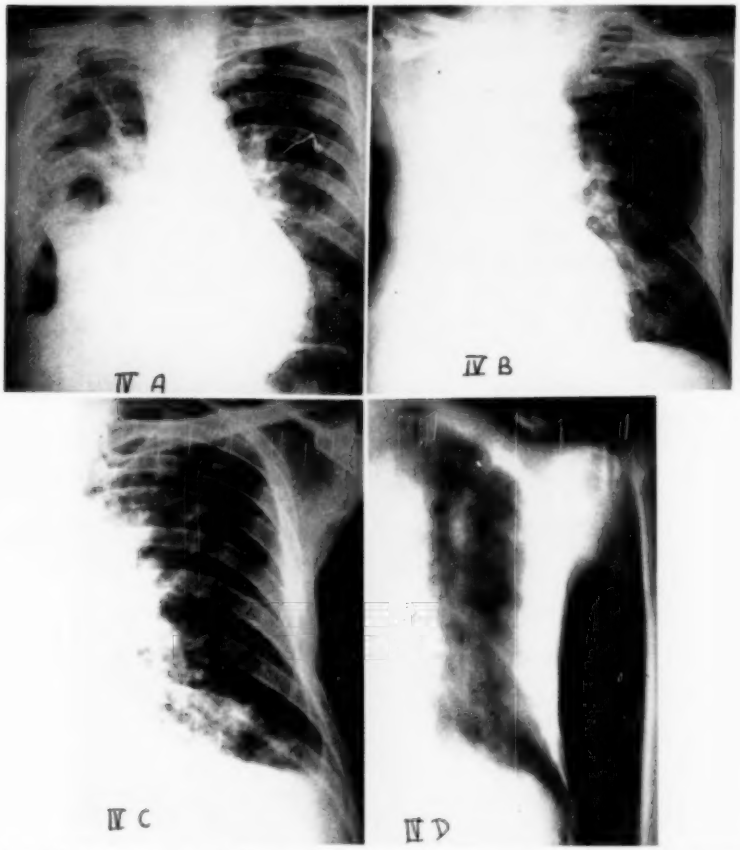


FIG. IVA. October 20, 1947. Hydropneumothorax and consolidation of lower half of right lung; multiple abscess cavities are present.

FIG. IVB. November 24, 1948, prior to discharge from hospital; evidence of right pneumonectomy and thoracoplasty; left lung is free of disease.

FIG. IVC. August 2, 1949. An infiltration radiating from hilum into the first and second intercostal spaces; small areas of rarefaction are seen within this density.

FIG. IVD. August 10, 1949. Tomogram; clearer visualization of the infiltration in left upper lobe.

bovis. He underwent intercostal drainage, pleural decortication, and pneumonectomy followed by thoracoplasty. The left lung was free of disease upon his discharge from the hospital.

He returned with an acute exudative tuberculous lesion involving the left upper lobe. The sputum was positive for acid-fast bacilli. The tuberculous lesion in the left upper lobe developed within sixteen months following the completion of the right pneumonectomy.

DISCUSSION

Table 1 summarizes the essential findings in the 4 cases presented. Two patients underwent lingulectomy and left lower lobe lobectomy for bronchiectasis. The third patient had a right middle and right lower lobe lobectomy for endobronchial sarcoidosis. The fourth patient had a right pneumonectomy for extensive actinomycotic disease. Neither the preoperative chest films nor those taken prior to discharge from the hospital showed any evidence of tuberculous disease. The sputum in each case prior to the operation was negative for acid-fast bacilli.

TABLE 1

Summary of Essential Findings

CASE	AGE	RACE	INITIAL DISEASE AND LOCATION	SURGICAL THERAPY	TIME INTERVAL BETWEEN FINAL RESECTION AND DEVELOPMENT OF TUBERCULOSIS	TYPE AND LOCATION OF TUBERCULOUS DISEASE
1	27	W	Bronchiectasis; lingula, LLL	Lingulectomy, LLL lobectomy	5 months	Caseous—pneumonic, advanced, cavitation, LUL
2	23	W	Bronchiectasis; lingula, LLL	Lingulectomy, LLL lobectomy	10 months	Caseous—pneumonic, advanced, cavitation, LUL
3	29	N	Endobronchial sarcoidosis, RLL	Lobectomy, RLL, RML	11 months	Caseous—pneumonic, advanced, cavitation, RUL
4	51	N	Actinomycosis, pyopneumothorax, right	Pneumonectomy, thoracoplasty, right	16 months	Exudative, moderate—LUL

The pulmonary tuberculosis manifested itself within five to sixteen months following the last operative procedure. The disease, when first detected, was, in the first three cases, far advanced, caseous-pneumonic in type with cavitation, and involved the remaining overdistended upper lobe on the ipsilateral side. In the fourth case the tuberculosis was moderate and exudative in type.

The development of tuberculosis may represent a coincidental exogenous reinfection with no direct relation to the operation. It is recognized that in the ordinary course of events a certain number of young adults will fall victims to the disease. However, the invariable appearance of tuberculous disease in the remaining portion of the upper lobe in the patients who underwent partial resection, the relatively acute onset, and the fulminating nature of the disease, all point toward a causal relationship.

Resection of pulmonary tissue results in hypertrophy and overdistention of the remaining lobes and contralateral lung. Birath *et al.* (1) have demonstrated that after pneumonectomy the volume of the remaining lung exceeded the calculated

normal values by about fifteen per cent. The functional residual air was approximately fifty per cent higher than the predicted value for a normal lung. Cournand and Berry (5) investigated the cardiopulmonary function in patients who underwent pneumonectomy or lobectomy, and found a reduction in the maximum breathing capacity that was not proportional to the diminished lung volume, but was in a large measure dependent upon the state of the overdistention of the remaining lung tissue. Opinion still varies as to whether pulmonary resection results in emphysema with atrophy and rupture of the alveolar septa of the remaining lung tissue, or in simple compensatory overdistention of the parenchyma without destruction of the elastic tissue.

The overdistention of the remaining lung parenchyma, as well as the manipulation of the lung during the operative procedure, may serve as a form of trauma in the setting up of a *locus minoris resistentiae* for an exogenous reinfection or an endogenous activation of a latent tuberculous focus. Rich (6) cited observations to indicate that trauma can activate a latent or quiescent tuberculous infection into active disease. The overdistention of lung tissue may result in the breaking open of inactive tuberculous foci, with the consequent liberation and dissemination of the contained bacilli to uninvolved pulmonary tissue. Pagel and MacCallum (7) have described the traumatic rupture of encapsulated caseous, fibrotic, and calcified tuberculous foci in the lung, with spread of the disease to fresh sites. Reichle and Gallavan (8) also stress the possibility of reactivation of a primary complex as a source of tuberculous reinfection.

Resistance to tuberculous infection undergoes considerable fluctuation. A tuberculous lesion that has been arrested or quiescent for a period of time often becomes reactivated under conditions which depress the patient's resistance. Baldwin, Petroff, and Gardner (9) claimed that bronchitis, influenza, and bronchopneumonia are commonly responsible for the reactivation and extension of unrecognized tuberculous disease into clinical activity. Pagel (10) described a case in which liquefaction of a caseous focus was caused by an invasion of pneumococci and leukocytes from an adjacent nontuberculous pneumonic process. He thus demonstrated that quiescent foci may reactivate into active disease after a nonspecific inflammatory process of the lungs.

Mediastinal fibrosis and fixation are frequent complications of pulmonary resection. The lymphatics within the lung drain towards the hilum; thus interference with lymph drainage may result. Therefore bacilli will not readily escape from the lungs, but accumulate to produce disease. According to Gardner (11) and Cummins (12) the interference in pulmonary lymphatic drainage secondary to the fibrosis in silicosis may account for either an increase in the susceptibility of silicotics to tuberculous infection or the reactivation of previously existing quiescent lesions.

SUMMARY

1. The case records of 4 patients who underwent pulmonary resection for nontuberculous disease, and who later developed active pulmonary tuberculosis, are presented.

2. Three patients underwent partial resection; the subsequent tuberculous

disease was advanced, caseous-pneumonic in type, and involved the overdistended portion of the remaining lung tissue on the ipsilateral side.

3. It is of interest that the chest roentgenograms of these patients on discharge from the hospital showed no evidence of tuberculosis. The pulmonary tuberculosis became manifest within five to sixteen months after the operation.

4. The need for a careful follow-up program, including frequent chest roentgenographic studies, for patients subjected to pulmonary resection is emphasized.

SUMARIO

Aparición de Tuberculosis Pulmonar consecutivamente a Ezcisión Pulmonar por Afección no Tuberculosa

1. En 4 casos sometidos a la resección pulmonar por afección no tuberculosa, luego se presentó tuberculosis pulmonar activa.

2. En 3 casos la resección fué parcial, pero la tuberculosis subsiguiente fué avanzada, de forma caseoneumónica, afectando la porción hiperdistendida del restante tejido del pulmón ipsilateral.

3. Resulta interesante que las radiografías torácicas de esos enfermos al ser dados de alta del hospital no revelaban signos de tuberculosis. La tuberculosis pulmonar se manifestó de cinco a dieciséis meses después de la operación.

4. Recálcase la necesidad de un cuidadoso plan de observación subsiguiente, incluso frecuentes estudios radiográficos del tórax, en los casos sometidos a una resección pulmonar.

Acknowledgment

The surgical procedures referred to in these cases were performed by Dr. J. Maxwell Chamberlain.

REFERENCES

(1) Overholt, R. H.: Pneumonectomy for malignant and suppurative disease of the lung, J. Thoracic Surg., 1939, *9*, 17.
(2) Churchill, E. D.: Lobectomy and pneumonectomy, J. Thoracic Surg., 1937, *6*, 286.
(3) Meade, R. H., Jr., Kay, E. B., and Hughes, F. A., Jr.: Report of one hundred and ninety-six lobectomies performed at Kennedy General Hospital Chest Surgical Center from 1942 to 1946, with one death, J. Thoracic Surg., 1947, *16*, 16.
(4) Birath, G., Crafoord, C., and Rudstrom, P.: Pulmonary function after pneumonectomy and lobectomy, J. Thoracic Surg., 1947, *16*, 492.
(5) Courmand, A., and Berry, F. B.: The effect of pneumonectomy upon the cardiopulmonary function in adult patients, Ann. Surg., 1942, *116*, 532.
(6) Rich, A. R.: The Pathogenesis of Tuberculosis, Springfield, Ill., C. C Thomas, 1946.
(7) Pagel, W., and Mac Callum, D.: On perifocal and traumatic hemorrhages in pulmonary tuberculosis, Brit. J. Tubere., 1946, *30*, 25.
(8) Reichle, H. S., and Gallavan, M.: Reactivation of a primary tuberculous complex as a source of tuberculous reinfection, Arch. Path., 1937, *24*, 201.
(9) Baldwin, E. R., Petroff, S. A., and Gardner, L. U.: Tuberculosis, Philadelphia, Lea and Febiger, 1927.
(10) Pagel, W.: Reactivation of a tuberculous focus by micro-organisms other than the tubercle bacillus, Lancet, 1937, *1*, 1279.
(11) Gardner, L. U.: Pneumoconiosis, Internat. Clin., 1935, *2*, 15.
(12) Cummins, S. L.: Silicosis in coal miners, Am. Rev. Tubere., 1934, *29*, 17.

PLEURAL, PERITONEAL, AND PERICARDIAL TUBERCULOSIS[1, 2, 3]

A Review of 209 Cases Uncomplicated by Treatment or Secondary Infection

OSCAR AUERBACH

(Received for publication November 9, 1949)

Renderath in 1927 (1) stated that, in spite of the abundant literature on tuberculosis of the various organs, only a few writers discussed tuberculosis of the serous surfaces. Although since that time there have been reports concerned with tuberculosis of the individual serous cavities, Renderath's statement is still essentially correct.

The present study has been undertaken to evaluate this little known condition in an attempt to correlate it with the other phases of tuberculosis in the body.

Material

All cases of tuberculosis which were examined post mortem were studied for the presence of tuberculosis of the serous membranes in three cavities; namely, peritoneal, pleural, and pericardial. Only those were chosen in which there was unequivocal evidence of active tuberculous disease. Fibrous thickening and adhesions of the peritoneal, pleural, or pericardial surfaces were not included since other inflammatory processes may cause similar changes.

Also excluded from this series were those cases in which the serosal tuberculosis was the result of the rupture of a pulmonary or intestinal focus into the pleural or peritoneal spaces. The reason for exclusion of these cases is that serositis resulting from the rupture of a pulmonary cavity into the pleural space or a perforation of an intestinal ulcer is complicated by the mixed infection which results when other microorganisms accompany tubercle bacilli. The dominant features of the resulting mixed infection are frequently caused by secondary bacterial invaders.

No case was included in which there had been an artificial pneumothorax on the affected side. Very often, at least in cases examined at autopsy, an exudate develops after the pneumothorax has been established. Whenever a tuberculosis of the pleura exists in this situation, it is most often, if not always, the result of an extension of a subpleural focus to the pleural surface. This presumably would not have occurred if the space had not been present.

It is realized that any attempt to set up arbitrary limits to serosal surface tuberculosis will meet with criticism, but an attempt has been made to select only those cases which occur in the natural course of the disease, uncomplicated by treatment or mixed infection.

[1] From the Laboratory Service, Halloran VA Hospital, Staten Island, New York.

[2] This material was collected while the author was at Sea View Hospital, Staten Island, New York.

[3] Sponsored by Veterans Administration and published with approval of Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect opinion or policy of the Veterans Administration.

Incidence: Two thousand three hundred thirty-three cases of tuberculosis were examined; of these, 209 (8.9 per cent) showed the presence of tuberculosis of the serous surfaces. In the majority of cases (160, 76.6 per cent) the involvement was limited to one serous surface. In 44 (21.0 per cent) tuberculosis was present in two serous surfaces, and in 5 (2.4 per cent) three membranes were affected.

Distribution: It may be seen from table 1 that the peritoneal surface is most frequently affected (131 cases). Following in order are the pleural (103 cases), and the pericardial (29 cases).

Age: In table 2 is shown the age distribution in the series. The majority of patients (124) were between twenty and thirty-nine years of age.

Sex: One hundred twenty-nine (61.7 per cent) males and eighty (38.3 per cent) females were in this series. There was a relatively larger number of women on this service than in the general autopsy series (28.5 per cent).

TABLE 1

Distribution of Serosal Tuberculosis

Peritoneum	90
Pleura	55
Pericardium	15
Peritoneum and pleura	35
Pleura and pericardium	8
Peritoneum and pericardium	1
Pleura, peritoneum, and pericardium	5
Total	209

TABLE 2

Age in Years

	AGE						
	1 to 10	11 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69
Number of cases	17	22	69	55	29	10	7

Color: Negroes were affected by the tuberculous process 139 times (66.5 per cent); whites, 68 times (32.6 per cent); and Asiatics, twice (0.9 per cent). This varies greatly from the over-all autopsy series in which there were 61.3 per cent whites and 37.6 per cent Negroes.

Associated extraserosal tuberculosis—pulmonary lesions: In 16 cases the lungs were normal except for the presence of healed remnants of a primary complex, while in 11 others they had apparently remained involved until shortly before death, when pulmonary tuberculosis resulted from the rupture of a softened caseous lymph node into the trachea or major bronchi.

A progressive primary complex was present in 7 patients, and in one case a healing primary complex was observed with healing miliary foci in both lungs. These findings were observed only in children.

An acute generalized miliary tuberculosis unaccompanied by chronic pulmonary tuberculosis was observed in 72 cases. In 15 of these, extensive healing of the miliary foci had occurred and miliary foci were few in number and best seen in the superior portions of the upper lobes of the lungs.

Chronic pulmonary tuberculosis was present in the remaining 102 cases and in 40 of these an accompanying miliary seeding in the lung parenchyma was noted which was part of an acute generalized miliary tuberculosis involving other organs.

Extrapulmonary tuberculosis: The two main organ systems involved were skeletal and urogenital. Tuberculosis of this type was present in 114 cases. Skeletal tuberculosis alone occurred in 39 cases, urogenital alone in 53, and in 22 both systems were involved.

TUBERCULOUS PERITONITIS

In 90 instances the peritoneal surface alone was involved by the tuberculous process. In an additional 41 cases a concomitant infection of one or more other serous surfaces was present.

Sex: There were seventy-six females and fifty-five males with tuberculous peritonitis. The preponderance of women is out of proportion both to the number of women in the autopsy series and to the number of women with serosal tuberculosis.

Color: Eighty-eight of the patients in this group were Negroes, 42 were white, and one was Asiatic. This is a slightly higher proportion of Negroes than in the entire group of serosal tuberculosis.

Associated urogenital tuberculosis: In more than one-third of the cases (57) of peritoneal involvement an active tuberculosis of some portion of the urogenital system was found. This showed an uneven distribution, with 41 occurring in women and 16 in men.

Renal tuberculosis as the sole involvement was present in only 3 of the cases, one occurring in a woman and 2 in men. In 4 other instances it was associated with a genital tuberculosis, 2 in women and 2 in men.

The Fallopian tubes were affected in all 40 cases of genital tuberculosis in women. In 38 of these there was an extensive involvement of the entire wall and a matting together of the neighboring structures. Here the most severe caseous tuberculosis of the peritoneum was in the region of the genital organs. In 2 others the tuberculous process within the wall of the Fallopian tubes was limited to ulceration or occasional foci within the inner aspects of the wall. In the latter case there appeared to be no direct relationship between the tubal and peritoneal tuberculosis.

Associated skeletal tuberculosis: Skeletal tuberculosis was present twenty-two times, and in all cases was associated with soft tissue abscesses and or fistulas. The peritoneal tuberculosis in almost all of these cases was that of an acute generalized miliary tuberculosis.

Origin of Infection

There appear to be two possible modes of infection of the peritoneal surface. One of these is by direct extension from a neighboring active tuberculous process; the other is a hematogenous dissemination from tuberculosis within some organ system.

In most instances the mode of development could be proved quite conclusively. In some, however, it could not be proved with any degree of certainty.

Direct Extension

Fallopian tubes: In 38 of the cases in this series the process was secondary to an extensive caseous tuberculosis of the Fallopian tubes. The peritoneal infection

apparently developed when the tubal tuberculosis extended to the serosal surface, whence it extended to the remaining surface. For this reason the most marked involvement was noted in the region of the matted genital organs. This variation in intensity was more prominent in the early cases before extensive progression had occurred.

In no instance was the prostate or kidney a source of serosal tuberculosis by direct extension.

Intestine: In 28 cases peritoneal tuberculosis was secondary to intestinal tuberculosis. In these cases the tuberculous process extending to the peritoneal surface was not limited to the region of the ulcers, but was present over the entire peritoneum. The intestinal involvement in most of these cases was extensive and manifested by deep penetrating ulcers. Often there was a diffuse seeding of grey or grey-yellow nodules over the peritoneum. These nodules measured from 1 to 3 mm. in diameter. The viscera were frequently lightly matted together by the slight fibrinous exudate which was also present. Although there were usually only small amounts of fluid within the peritoneal cavity, occasionally as much as 500 cc. of clear to slightly cloudy yellow fluid were present. Chronic pulmonary tuberculosis was the only other tuberculosis present in addition to the intestinal involvement in these cases.

Pleura: Extension from a pleural tuberculosis occurred in 11 cases. In these the pleura was much more extensively affected than the peritoneum and in some the process was limited to the region of the diaphragm, the perisplenic and the perihepatic tissue. Thus there was a decrease in intensity from above downwards. The extension to the peritoneal surface occurred through the diaphragm, with caseous foci developing along the course of lymphatic vessels.

Hematogenous Tuberculosis

Blood-stream dissemination from an active extraserosal tuberculosis occurred in 38 cases. In all but 2 patients either an active skeletal or urogenital tuberculosis was found and in 2 instances a primary complex was present. These extraserosal lesions were clinically and anatomically older than the peritoneal tuberculosis. In all instances the peritoneal lesions were of miliary type.

Isolated Peritoneal Tuberculosis

In 16 cases the peritoneal tuberculosis was the oldest process, except for the healed primary complex. Peritoneal tuberculosis occurred with pleural tuberculosis in 4 instances, with pericardial tuberculosis in one. In 4 patients involvement of all three membranes was present, and in 7 patients the peritoneum was the only surface so involved. The mesenteric lymph nodes were enlarged and caseous. In 8 of these patients an acute generalized miliary tuberculosis was the terminal episode.

TUBERCULOUS PLEURITIS

Involvement of the pleura occurred as a sole serosal involvement in 55 instances, while in the remaining 48 it occurred in combination with a tuberculous involvement of one or more of the other serous surfaces.

Sex: There were 75 males in this group and 28 females. This parallels very closely the sex distribution in the general autopsy series.

Color: The majority of patients were Negroes (84), while 18 were white, and one was Asiatic. Thus, there was a greater proportion of Negroes than in the entire series of serosal tuberculosis.

Associated urogenital tuberculosis: An associated urogenital tuberculosis was present in 23 cases. This is considerably less than in peritoneal tuberculosis.

In contrast to peritoneal tuberculosis, 17 cases of pleuritis occurred in men and only 6 in women. Of the 6 which occurred in women, 4 were instances of combined peritoneal and pleural tuberculosis in which the serosal tuberculosis began in the Fallopian tubes.

Nineteen of the cases were those of genital tuberculosis and 4 were limited to the urinary system.

Associated skeletal tuberculosis: Skeletal tuberculosis was present thirty-two times. This is proportionately a greater incidence than that found in peritoneal tuberculosis.

Distribution: A bilateral disease was present forty-two times. In the 61 instances when unilateral disease was present the right side was involved thirty-three times and the left side twenty-eight times.

There is a striking difference in the relationship between the unilateral and bilateral disease and the mode of origin. In bilateral involvement only 8 cases occurred as a result of direction extension. The lung was the source of the infection in 7 of these patients and the peritoneum in one. In 23 it resulted from a hematogenous dissemination while in 11 it occurred as an isolated disease.

In unilateral infection, on the other hand, direct extension was responsible for the disease in 33 cases. The serosal disease was derived from the lung in 28 cases, the peritoneum in 4, and the chest wall in one. The hematogenous route accounted for 22 cases while in 6 it was present as an isolated disease.

Origin of Infection

There are two main routes to be considered in the development of the tuberculous process in the pleura: (1) a direct extension either from a neighboring structure; or (2) a hematogenous infection from some distant focus.

Direct Extension from the Lungs, Peritoneum, and Chest Wall

Direct extension from the lungs occurred in 35 cases. Twenty-five of these patients had chronic pulmonary tuberculosis. This is a very small percentage of such cases when compared to the general autopsy series. It is striking that 20 were Negro patients in whom the pulmonary tuberculosis was of short duration (4 to 8 months) and rapidly progressive. In 10 patients the tuberculous pleuritis was secondary to a primary complex. In all but one of these the primary focus was of a progressive nature. The caseous involvement of the pleura in all instances was not confined to the region of the primary focus, but involved the entire aspect of the pleura (figure 2).

In 2 instances the pleural cavities became involved by the extension from

an advanced tuberculosis of the ribs. The caseous subperiosteal tissue extended irregularly into the pleura, so that the pleura when removed from the chest had an irregular motheaten appearance.

Peritoneal tuberculosis was the source in 5 cases; 4 of these had their origin in the Fallopian tubes and one in intestinal ulceration. The pleural tuberculosis was caseous in character, usually was limited to the inferior portions, and occasionally only to the diaphragmatic surface. The diaphragm was thickened by numerous caseous foci throughout its wall.

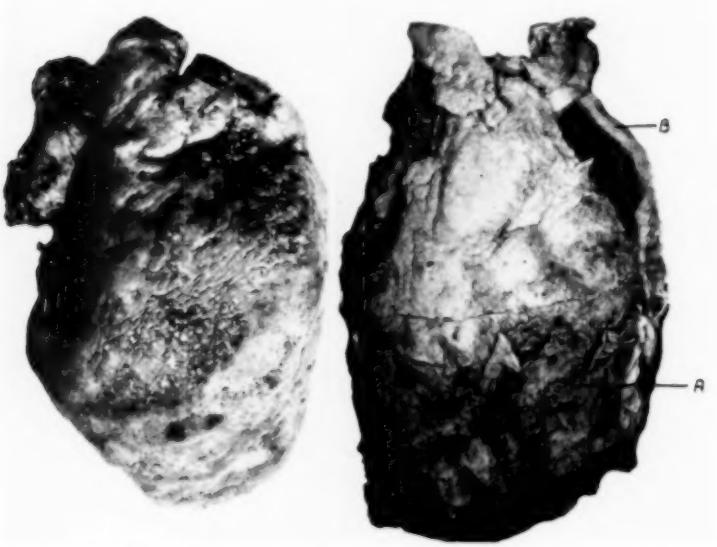


FIG. 1A. (Left) Tuberculous pericarditis in a 25-year-old man. The visceral surface is covered by a "shaggy fibrinous exudate."

FIG. 1B. (Right) Tuberculous pericarditis in a 36-year-old man. The superficial surface is lined by a thick fibrinous exudate (a), beneath which is a wide zone of caseation (b).

Hematogenous Dissemination

This was the more common route by which the pleura was infected (46 times). The seeding to the pleura occurred from an active extrapleural tuberculosis (skeletal and/or urogenital).

Isolated Pleural Tuberculosis

In 15 instances the caseous pleural tuberculosis was the oldest active process aside from the healed primary complex. This occurred alone six times, with peritoneal tuberculosis four times, with pericardial tuberculosis once. In 4 cases

all three serosal surfaces were involved. The tracheobronchial lymph nodes were invariably enlarged and caseous. An acute miliary tuberculosis as a final episode was found in 8 of these cases.

FIG. 2. Caseous pleuritis in a 4-year-old boy occurring by a direct extension from a progressive primary focus in the upper lobe.

TUBERCULOUS PERICARDITIS

Sex: There were 22 males and 7 females in the group with tuberculous pericarditis.

Color: Fourteen of the patients were whites and fifteen were Negroes. Although there is a greater proportion of Negroes than in the general autopsy series, it is not as great as that in peritoneal and pleural tuberculosis.

Associated skeletal and urogenital tuberculosis: Skeletal or urogenital tuberculosis was present in 15 of the 29 cases. Skeletal tuberculosis occurred eight times, urogenital tuberculosis alone three times, and in four instances both systems were affected. In all cases the tuberculosis in these organs was older than that in the pericardium.

Origin of Infection

As in the other forms of serosal tuberculosis, there are two routes by which tuberculous pericarditis may develop: (*1*) direct extension, (*2*) hematogenous seeding.

Direct Extension

In 8 patients the origin of the pericardial infection presumably occurred by direct extension. Two were individuals with tuberculoma of the myocardium. The tuberculous process in both the myocardium and pericardium was so advanced that it could not be anatomically ascertained which was the older lesion. In both instances the caseous pericarditis was in an area directly continuous with the tuberculoma of the myocardium. The origin of the cardiac tuberculosis in both instances was the result of a hematogenous dissemination.

Two of the other persons showed a tuberculosis of the pericardium limited to the parietal aspect on one side. This was in direct contiguity with a more advanced caseous tuberculosis of the pleura on that side.

In 4 patients the tuberculous process involved the entire pericardial cavity, but was clinically and anatomically more recent than a co-existent pleural tuberculosis.

Hematogenous Origin

In 13 cases the route of infection was through the blood stream from a urogenital or skeletal tuberculosis. Clinically and anatomically the extrapericardial tuberculosis was older than the pericardial tuberculosis.

Isolated Pericardial Tuberculosis

There were 8 instances in which the pericardial tuberculosis, either alone or associated with other serosal tuberculosis, was the oldest tuberculous process in the body, aside from a healed primary complex. The lesion within the pericardium was one which from its pathologic character appeared to have been present for a considerable period of time. In the 6 instances where this was associated with other serosal tuberculosis, because of the advanced stage of development of the lesions, it could not be established whether the process began in one membrane and continued to another, or whether it developed in both simultaneously.

An acute generalized miliary tuberculosis was a fatal complication in 3 of these cases.

Pathologic Findings

The gross and microscopic changes in the peritoneal, pleural, and pericardial cavities were similar.

GROSS APPEARANCE

There were two main forms which were observed at autopsy: (*1*) caseous tuberculosis; and (*2*) generalized miliary tuberculosis.

Caseous tuberculosis: Caseous tuberculosis was by far the more frequent type found in the present series. The early stage, infrequently observed at

FIG. 3. (Upper) Caseous pleuritis (left) which developed in a 36-year-old man who had extensive tuberculosis of the spine. Caseous nodules (not present in this view) were also present in the visceral and parietal pleurae on the right. The tracheobronchial lymph nodes are enlarged and caseous.

FIG. 4. (Lower) Caseous calcified tuberculous pleuritis (left) in a 54-year-old man with skeletal tuberculosis in many regions. A miliary tuberculosis is present especially marked in the noncompressed right lung.

autopsy, was characterized by a slightly thickened serosal membrane covered by a variably wide layer of fibrin. When a fibrinous exudate was present on the

visceral pericardium it caused a shaggy appearance, the well-known "bread and butter heart" (figure 1A). The exudate within the lumen was of variable character, but generally was rich in fibrin. The fluid was usually clear, but at times was also gelatinous. Sometimes blood was present, and occasionally it was so extensive as to give the exudate a hemorrhagic appearance. A serosanguinous appearance was seen only in pleural and pericardial tuberculosis in this series. The tuberculous nature of the disease was first ascertained on microscopic examination.

It appeared that the fibrinous layer had soon been transformed into a caseous layer. As the process continued the serous surface was covered by an increasingly thick zone of caseation (figure 1B). Where the space was patent, the lumen contained large amounts of fluid rich in fibrin which frequently had a gelatinous appearance (figure 3).

In many cases the space was obliterated by the caseous exudate. The thickness of the caseous layer seemed to depend upon the massiveness of the infection and the stage of anatomic healing, and varied from 2 mm. to 2 cm.

In the early stages the zone of caseation was surrounded by a narrow red area followed by a thin grey membrane. Later the outer zone, both in the visceral and parietal layers, became thickened and grey-white in appearance. This was more marked in the parietal layer where it reached a thickness of 1 to 2 cm. in long-standing cases.

The caseation which presumably was soft at first became firm in consistency and, as healing continued, became partially calcified. When the process continued to complete healing, the calcium deposits were massive (figure 4). When the space remained patent, fragmented calcium particles were attached to the surface and sometimes lay free within the lumen. When the space was obliterated, a narrow, stony, hard, yellow layer was present between the greatly thickened visceral and parietal layers which were grey-white in appearance.

Generalized miliary tuberculosis: Miliary foci on the serous surfaces were yellow to grey nodules which varied from 1 mm. to 3 mm. in diameter. Although the foci projected above the surface, their location was beneath the mesothelial lining. Small amounts of fibrin were present on the serosal surface. The serosal cavity usually contained only small amounts of clear yellow to cloudy, amber fluid (15 to 50 cc.); occasionally it contained 1,000 cc. or more. The fibrin and fluid appeared to be a reaction to the development of tubercles within the underlying serosal tissue.

The abdominal viscera were frequently lightly matted together and easily separable from one another. When the serosal exudate had been replaced by fibrous tissue such separation was no longer possible. Similarly, both surfaces in the pleural cavity were firmly adherent. These adhesions were not evenly distributed, nor did they always occur in these cases, since their formation was dependent upon the presence of fibrin on the serosal surface.

MICROSCOPIC APPEARANCE

Caseous tuberculosis: The earliest change was the appearance of a serofibrinous exudate on the serous surfaces. Within the network of fibrin were many poly-

morphonuclear leukocytes and erythrocytes. In many instances the mesothelial lining underlying the exudate was still intact, so that one gained the impression that the exudate had originated in another zone and had extended toward these areas. The exudate was generally extensive and the portion lying near the serosal surface apparently underwent necrosis very soon. The nuclear fragments of the necrotic cells gave the material a blue granular appearance. The fibrin was swollen and retained a pink granular stain. Towards the lumen the fibrinocellular exudate remained intact.

At the periphery of the caseation within the submesothelial tissue, there was a narrow area of vascular granulation tissue composed of dilated capillaries, fibroblasts, epithelioid cells, and Langhans' giant cells. This granulation tissue, as it extended into the peripheral portion of the caseation, destroyed much of the serosal membrane. Subsequently all of the fibrinous exudate within the lumen underwent caseation and added to the thickness of the caseous zone. In some instances the lumen of the cavity was obliterated by the caseous exudate.

Where healing had taken place, the zone of vascular granulation tissue which invaded the peripheral portions of caseation extended through and apparently replaced all of the caseous material. This occurred when the zone of caseation was thin. Where the width of the caseous layer varied, the thinnest portions were completely replaced by vascular granulation tissue, the thicker portions being only partially replaced. This resulted in isolated enclosed zones of caseation.

It appeared that as the collagen fibers within the granulation tissue increased the cells and capillaries gradually disappeared. Finally a wide zone of hyalinized connective tissue surrounded the caseation. Concomitantly calcium salts were laid down in the area of caseation. This at first was finely granular, and later became quite dense. If the granulation tissue invasion of the zone of caseation was complete, a zone of hyalinized connective tissue resulted in which all signs of specificity were lost.

Generalized miliary tuberculosis: This form of tuberculosis differed from the caseous type in that it was present beneath the serosal membrane in the form of oval, round, and sometimes irregular foci of small size. These were epithelioid giant cell tubercles, the larger of which contained small central zones of caseation. Lying on the serosal surface were small amounts of fibrin containing a few polymorphonuclear leukocytes, erythrocytes, and mononuclear cells. The foci caused a slight protrusion of the superficial surface but usually did not rupture through it.

These foci apparently may heal completely. Peritoneal tissue removed at many abdominal operations has shown the presence of miliary tubercles. Subsequently, either at autopsy or at a subsequent operation, there was a complete disappearance of the tuberculous process. The tubercles heal by an increase in collagen fibrils. This results in a fibrous tissue which is fused with the surrounding serosal connective tissue. The fibrinous exudate may be absorbed completely or partially. That which remains may be invaded and replaced by granulation tissue from the underlying tissue, leaving a slightly thickened serosa in these regions.

Discussion

The overwhelming preponderance of Negroes with serosal tuberculosis is a striking feature of this disease. There are two main reasons for this: (*1*) the greater tendency for Negroes to develop both skeletal and urogenital tuberculosis and (*2*) rapid forms of tuberculosis are observed more frequently in Negroes.

Both skeletal and urogenital tuberculosis occur relatively more frequently in Negroes. It is believed that most of these cases are related to the development of larger primary foci in the Negro, so that there is a greater tendency to blood-stream dissemination to these organs. The development of serosal tuberculosis in many instances is the result of a hematogenous dissemination from these organs. Tubal tuberculosis accounts for a portion of the cases of peritoneal tuberculosis by direct extension.

The studies in the present report clearly show that the more rapidly progressing forms of tuberculosis have a much greater tendency to develop in Negroes. This has been true, both in regard to the primary complex and to chronic pulmonary tuberculosis. This tendency towards rapid progression makes a spread to the adjacent pleural surfaces more likely in Negro patients.

There is a greater incidence of serosal involvement in women in the present series than in the general autopsy series from this institution. An analysis of the sex distribution in the three forms of serosal involvement shows a striking contrast between peritoneal tuberculosis on the one hand, and pleural and pericardial tuberculosis on the other. This is directly attributable to the fact that tuberculosis of the Fallopian tubes has a ready access to the abdominal cavity and accounts for many cases of peritoneal tuberculosis. The greater incidence of women with tuberculous peritonitis in the present series is of interest in that previous reports in the literature (Johnston (2) Faulkner and Everett (3)) state that the incidence at autopsy in contrast to operative statistics shows the disease to be more common in men.

There can be no uniform agreement as to what conditions to include under tuberculosis of the serosal surface, particularly pleural and peritoneal involvements. The inclusion of all cases of empyema of tuberculous origin and all cases of circumscribed serosal tubercles from intestinal ulceration would alter the incidence to a greater degree. Pleural tuberculosis would then comprise 20 per cent of the cases and peritoneal tuberculosis would only total 15 per cent. There would be no alteration in the incidence of pericardial tuberculosis. To emphasize this difficulty, the incidence of peritoneal tuberculosis in this series (5.6 per cent) differs considerably from the 11 per cent reported by Cummins (4) and the 16 per cent reported by Borschke (5) in autopsy studies on tuberculous patients.

The incidence of pericardial tuberculosis (1.2 per cent) in the present series is much less than the 5.9 per cent reported by Werner (6). The figures of Osler (7) and Norris (8), however, more closely approximate our own.

Although the source of serosal tuberculosis is clear in most instances, there are some cases in which it is difficult to explain it. The two main routes of the infection to the three surfaces are by direct extension and hematogenous dissemination from distant organs.

Direct extension is the most important source of peritoneal tuberculosis, accounting for 59 per cent of the cases. Only about 40 per cent of pleural, and 27 per cent of pericardial, tuberculosis develops in this manner. Direct extension can occur only from the organ beneath the serosal covering or from one serosal surface to another. Since extension from the underlying organ accounts for the great majority of these cases, the frequency of the serosal involvement will in part depend upon the frequency of tuberculosis in organs with serosal covering.

It should be borne in mind that the caseous tuberculosis within the lung must reach the serosal surface before the overlying serous cavity has been obliterated by fibrous tissue. This is extremely important and accounts for the fact that serosal tuberculosis occurs infrequently in spite of the great frequency of chronic pulmonary tuberculosis with its many caseous foci. Caseous foci which develop in the lung parenchyma are surrounded by a zone of perifocal reaction. When the foci develop close to the overlying pleura, the perifocal reaction within the pleural space is converted into connective tissue. This causes an obliteration of the pleural space. Thus, even though a cavity or a liquefied caseous focus subsequently may extend through this pleura, there can be no serosal tuberculosis because no breach is made in the pleural surface. In those cases, however, where there is a very rapidly progressing pulmonary tuberculosis or primary complex, the caseous foci within the lung may very soon extend into the overlying pleura.

Conditions are somewhat different in the abdominal cavity where the two main sources of direct extension are the Fallopian tubes and intestinal ulceration. In approximately 50 per cent of the cases of tubal tuberculosis there is an accompanying serosal involvement. Here the caseous process within the wall is advanced and extends rapidly through all layers to reach the peritoneal surface. The caseation on the visceral surface soon continues on to the neighboring structures (uterus, ovaries, and intestines), often matting these together.

The intestinal tract also lies freely exposed within the abdominal cavity and is not only affected many times more frequently than the Fallopian tubes, but contains many ulcers along its course. Thus the opportunity for serosal tuberculosis would appear to be much greater, but for a number of reasons it does not occur. Unlike tubal tuberculosis, in the majority of instances the disease is a slower and more chronic process with gradual progression from within outwards. When the ulcers are deep, an overlying thickened layer of serosal connective tissue forms the outer wall of the intestinal tract, while lymphatic channels in the serosa contain tubercles along its course to the regional mesenteric lymph nodes. The entire process is limited to the region of the ulcers. In a small group of cases (far advanced), the lymphatic drainage from the ulcers is not limited to the region of the ulcers, but is diffuse over the entire peritoneal surface.

In none of the cases of the present study was it possible to demonstrate the rupture of a caseous mesenteric lymph node or a caseous focus within the spleen as the mode of origin of peritoneal tuberculosis.

Hematogenous dissemination involves the pleural cavity more frequently than the peritoneal cavity. Signs and symptoms of pleuritis and peritonitis in these cases very often develop when the patient is under observation for skeletal or

urogenital tuberculosis. Roentgenographic examination in many instances will show the development of fluid in a previously clear chest.

There is also morphologic evidence in most instances that the serosal tuberculosis follows the urogenital or skeletal tuberculosis. Often the gross and microscopic findings of the serosal tuberculosis speak for a more recent origin than the distant organ tuberculosis and are quite evident when the serosal disease is of the miliary type. In the caseous forms the surrounding granulation tissue shows less evidence of healing changes than the extraserosal tuberculosis. Occasionally, however, the healing of serosal tuberculosis is so advanced that it is either difficult or impossible to determine a time relationship.

In favor of a hematogenous route is the high incidence of skeletal and urogenital tuberculosis in cases of serosal tuberculosis. Skeletal tuberculosis is present in 29.1 per cent in this series and in 10.1 per cent in the entire autopsy series. Similarly the incidence of male genital tuberculosis is also greater (20 .9 per cent) than in the general group (14.4 per cent). Female genital tuberculosis is not considered here since the mode of development from it is by direct extension.

Hematogenous dissemination generally results in the development of tuberculous foci in paired organs. One would then expect to see bilateral disease when the pleurae are involved through this route. There is a striking difference between the frequency of serosal tuberculosis of hematogenous origin in unilateral and bilateral disease (54 per cent in bilateral and 36 per cent in unilateral). Added support to the view that isolated serosal tuberculosis is hematogenous is the much greater tendency of the pleural tuberculosis to be bilateral in these cases.

The question arises as to why 36 per cent of the cases of unilateral disease occur by way of the blood stream. An attractive view is that the original blood-stream seeding involved both pleurae, but that on one side the disease progressed while the contralateral disease healed. An analogous situation obtains in renal tuberculosis. Despite seeding to both kidneys, unilateral chronic renal tuberculosis is more frequent than bilateral.

In the present study there were 25 cases of isolated serosal tuberculosis in which it was difficult to find an extraserosal source of disease. This is the type of case which has hitherto been reported as primary in origin. It is an accepted fact today, however, that tuberculosis occurring in a structure having no communication with the outside cannot be the site of a primary infection. In all of these cases there was a healed primary complex and an active serosal tuberculosis.

In 14 of these cases a terminal acute generalized miliary tuberculosis was also present. The hematogenous dissemination was undoubtedly the result of the blood-stream invasion from the accompanying extensive caseous regional lymph nodes. Where chronic pulmonary tuberculosis developed shortly before the patient's death, there appeared to be no direct relationship between it and the serosal tuberculosis.

There are two possible explanations for the appearance of isolated serosal tuberculosis. One possibility is that tuberculous involvement of the skeletal

system may have been overlooked since it is not possible to completely examine all of the bones at autopsy. This is difficult to accept because it is rare to find skeletal tuberculosis at autopsy without an accompanying abscess or fistula. The other and more likely possibility is that a late primary complex may have been the source of these cases. Twenty-one of the patients were Negroes and all but 2 had extensive caseation of the abdominal, the thoracic, and sometimes the cervical lymph nodes. The autopsies revealed that there is a greater tendency to large primary lesions with extensive hematogenous disseminations in this race. If, as the pulmonary focus was undergoing anatomic healing, the lymph node component of the complex were to progress, an extensive blood-stream dissemination of tubercle bacilli to the serous surfaces could occur.

There are some authors (Renderath (1), Huebschmann (9)) who agree that there are two forms of serosal tuberculosis, namely, miliary and caseous, but believe that these are stages of the same process. It is their view that the miliary tuberculosis is the milder form, while the caseous type is the result of a severe infection.

Huebschmann (9), in his discussion of tuberculous peritonitis, designates the milder form as the "dry" type and the more severe as the "moist." He states that there is no sharp division between the types and that all transition stages between the two may be observed. The "drier" forms progress to miliary tuberculosis without inflammation or the superficial surface. According to him, the "moist" form contains an abundant exudate from the onset. The exudate rich in fibrin is converted into caseation with extensive matting together of the structures.

On the basis of the pathologic findings in the present study, it is believed that the two types are different and are in great part dependent upon the mode of development of the serous tuberculosis. Where the tuberculous involvement of the serosal surface occurs by a direct extension from caseation within an organ, e.g., Fallopian tube, primary complex, chronic pulmonary tuberculosis, a caseous tuberculosis will develop within the serosal cavity. Less often, caseous tuberculosis may develop within a serous cavity (especially pleural) following a hematogenous dissemination. All cases of hematogenous dissemination were not characterized by miliary tubercles. In some instances, especially in the pleural cavity, the foci were large and had caseous centers. In these cases large foci within the serosal connective tissue extended to the free surface so that a caseous tuberculosis resulted.

No evidence of miliary tuberculosis within the pericardium was found. Orth (10) and Huebschmann (9), who had described this entity, believe that it occurs shortly before death as part of a generalized miliary tuberculosis. That not one such case was found in over 300 cases of acute generalized miliary tuberculosis serves to emphasize its rarity.

There is evidence both from clinical observations and autopsy studies that serosal tuberculosis may heal. There are reports (Lindner (11), Stubenbord and Spies (12)) of abdominal operations in which an extensive peritoneal tuberculosis was encountered and proved by tissue examination and bacteriologic

examinations, including animal inoculations. Subsequent operations or autopsies in many instances showed fibrous thickening of the serosal surface but no evidence of tuberculosis. Similar conditions prevail in both the pleural and pericardial cavities. The diagnosis in most of the latter cases is made by the roentgenographic observation of increased fluid and the finding of organisms within aspirated material from these cavities. Subsequent autopsy examination of cases showing anatomic healing reveals a fibrous thickening of the serosal layers with adhesion and obliteration of the space. Narrow zones of caseation containing calcium may be present in some of the cases. In others no caseation is present.

There are two problems which present themselves: (*1*) Under what conditions does healing of serosal tuberculosis occur? (*2*) Are there any available criteria which make it possible to diagnose a tuberculous etiology if the lesion has reached the end stage of healing?

The vast majority of cases within this series are those in which the underlying disease causing the serosal tuberculosis was in a progressive stage of development. In some instances also, the serosal tuberculosis apparently progressed although the original source had healed. There was, however, another group of cases in which the serosal tuberculosis completely healed, whether or not there was healing of the disease from which it arose. This may occur in any of the serosal cavities and it is difficult to attempt to estimate the frequency of occurrence. As we have already pointed out, there is ample evidence that healing does take place.

Since any inflammatory process may also result in an adhesion and the obliteration of the serosal cavity, we are not justified in classifying all cases as tuberculous in which these findings are present. It is our impression that a correlation of the clinical observations with the autopsy findings will identify the majority of cases which are of tuberculous origin. This is especially true if there has been an extensive zone of unorganized caseation containing calcium.

Summary

1. Peritoneal, pleural, and pericardial tuberculosis are present in 8.9 per cent of all tuberculous autopsies with 61.7 per cent being found in males and 38.3 per cent in females. There is a great tendency for this disease to develop in Negroes.

2. The serosal disease develops either through direct extension from a neighboring visceral tuberculosis or by way of the blood stream.

3. Active tuberculosis of these surfaces may exist as an isolated disease.

4. The gross and microscopic appearance at all three sites is similar. Two main types may be distinguished: a) caseous tuberculosis, b) miliary tuberculosis.

5. Healing may occur with scar tissue formation and obliteration of the space. Sometimes areas of caseation become encapsulated by the scar tissue and undergo calcification. Healing of serosal tuberculosis is most likely to occur if the underlying organ tuberculosis also heals.

Sumario

Tuberculosis Pleural, Peritoneal y Pericardíaca: Repaso de 209 Casos no Complicados por la Terapéutica o la Infección Secundaria

1. Hubo presente tuberculosis peritoneal, pleural y pericardíaca en 8.9 por ciento de todas las autopsias realizadas en tuberculosos, correspondiendo 61.7 por ciento de los casos descubiertos a varones y 38.3 por ciento a mujeres. Estas manifestaciones muestran mucha tendencia a presentarse en los negros.

2. Esta serosopatía aparece bien por difusión directa de la tuberculosis de un órgano cercano o por propagación hemática.

3. La tuberculosis activa de dichas membranas puede existir en forma de enfermedad aislada.

4. El aspecto macro- y microscópico es semejante en los tres sitios mencionados, cabiendo distinguir dos formas principales: a) tuberculosis caseosa y b) granulia.

5. La curación puede ocurrir con formación de tejido cicatricial y obliteración del espacio afectado. A veces las zonas caseosas pueden ser encapsuladas por el tejido cicatricial y experimentar calcificación. La cicatrización de la tuberculosis de las serosas es más probable si también cicatriza la tuberculosis del órgano subyacente.

REFERENCES

(1) Renderath, E.: Zur Pathologischen Anatomie der Tuberkulose der serösen Haute, Virchows Arch. f. path. Anat., 1927, *266*, 475.

(2) Johnston, G. B., Kelly H. A. and Noble C. P.: Gynecology and Abdominal Surgery, Philadelphia, W. B. Saunders Company, 1910, *2*, 617.

(3) Faulkner, R. L., and Everett, H. S.: Tuberculous peritonitis: A statistical and clinical study of one hundred and eighty-seven cases, Arch. Surg., 1930, *20*, 664.

(4) Cummins, W. T.: Tuberculous peritonitis: A statistical review, Univ. Pennsylvania M. Bull., 1905-1906, *18*, 272.

(5) Borschke, M.: Pathogenese der peritonitis tuberculosa, Virchows Arch. f. path. Anat., 1892, *127*, 121.

(6) Werner, W. I.: Tuberculous pericarditis: With a report of three cases, Am. Rev. Tuberc., 1930, *21*, 202.

(7) Osler, W.: Tuberculous pericarditis, Am. J. M. Sc., 1893, *105*, 20.

(8) Norris, G. W.: Tuberculous pericarditis: Based upon a study of 7,219 autopsies in Philadelphia hospitals, Univ. Pennsylvania M. Bull., 1904, *17*, 155.

(9) Huebschmann, P.: Pathologische Anatomie der Tuberkulose, Berlin, Julius Springer, 1928.

(10) Horth, J.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, August Hirschwald, 1887, *1*, 137.

(11) Lindner, H.: Ueber die operative Behandlung der Bauchfelltuberculose, Deutsche Ztschr. f. Chir., 1892, *34*, 448.

(12) Stubenbord, J. G., and Spies, J.: Tuberculous peritonitis, Surg., Gynec. & Obst., 1938, *67*, 269.

INFLUENCE OF *p*-(Di-n-Propylsulfamyl)-BENZOIC ACID, "BENEMID," ON PARA-AMINOSALICYLIC ACID (PAS) PLASMA CONCENTRATIONS[1]

WILLIAM P. BOGER AND FORREST W. PITTS

(Received for publication March 23, 1950)

INTRODUCTION

A new compound, *p*-(di-n-propylsulfamyl)-benzoic acid, Benemid[2], has been submitted to clinical investigation after extensive toxicologic and pharmacologic studies. Benemid is a crystalline, white powder which is nearly insoluble in water. In mice the oral $L.D._{50}$ is 1,156 mg. per Kg. of body weight, and when injected subcutaneously the $L.D._{50}$ is 1,665 mg. per Kg. of body weight. Dogs have received as much as 200 mg. per Kg. of body weight per day for as long as six weeks without significant toxicity (1), so that 1 to 4 Gm. per day would appear to be a safe dose for administration to human subjects. In dogs the compound has been shown to be rapidly absorbed from the gastrointestinal tract and, following single oral doses, the drug may be demonstrable in the plasma for as long as thirty-six hours. Benemid is excreted almost entirely in a conjugated form, probably a glucuronide, and it is bound by plasma proteins to the extent of nearly 75 per cent. The pharmacologic action of Benemid appears to be the inhibition of an enzymatic system which inactivates a number of therapeutically effective compounds by conjugating them with glycine (1).

Preliminary studies in human subjects have shown that Benemid, in single doses of 1 to 2 Gm. or in a daily dose of 2 Gm. administered as 0.5 Gm. every six hours, is effective in enhancing plasma concentrations of penicillin two- to five-fold (2); and this degree of enhancement is the same as that observed with carinamide (3, 4, 5). On the basis of the similarity in effect of Benemid and carinamide on penicillin, it was decided to investigate the effect of Benemid in PAS. In some previous observations in this laboratory on carinamide and PAS, it had been found that plasma concentrations of PAS were enhanced by two to four times, and similar observations have been reported by other investigators (6, 7). It seemed appropriate, therefore, to investigate the effect of Benemid in PAS and the following study was undertaken.

PLAN OF INVESTIGATION

Seven patients with pulmonary tuberculosis who were receiving PAS as a part of their therapy and who were willing to cooperate in this study were chosen for investigation. The patients were in good general physical condition and presented no evidences of renal impairment as determined by the ordinary laboratory tests.

Each subject was compared with himself, under three sets of circumstances: (*1*) when sodium PAS was administered as a single 4 Gm. oral dose; (*2*) when a

[1] From Philadelphia General Hospital, Philadelphia, Pa.

[2] Benemid is the Sharp and Dohme, Inc. trademark for *p*-(di-n-propylsulfamyl)-benzoic acid. This drug has tentatively been given the chemical name "probenecid."

4 Gm. dose of sodium PAS was administered in conjunction with a single oral 2 Gm. dose of Benemid; and, (*3*) when Benemid in a dose of 0.5 Gm. was administered at six-hour intervals for twenty-four hours prior to the oral administration of 4 Gm. of sodium PAS. Blood samples were drawn at one-half, two, four, six, and eight hours after the administration of sodium PAS. All samples were drawn into heparinized syringes, the plasma freed from cells by centrifugation, and the plasma harvested and stored at −20° C. until plasma determinations of PAS were done. Intervals of two to five days intervened between the tests done on the same patients. The plasma estimations of PAS were done by the method of Way (8) and it was determined by repeated tests that Benemid did not interfere with the Way method.

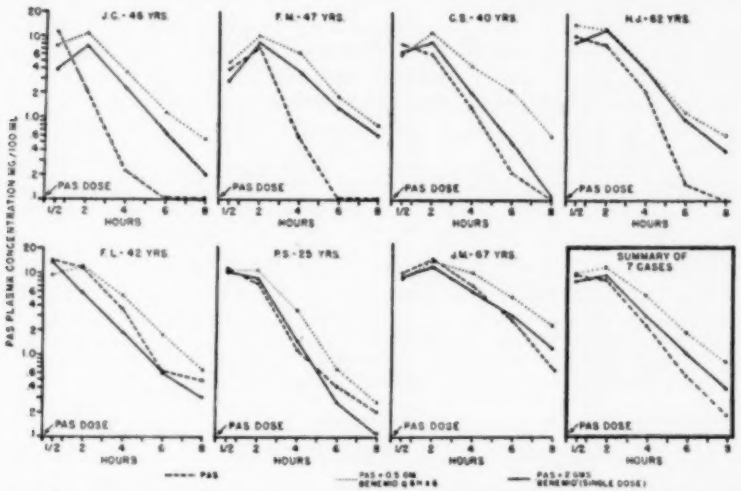


FIG. 1. PAS plasma concentrations after 4 Gm. sodium PAS modified by single and repeated doses of Benemid.

RESULTS

Both the individual and average results obtained are presented in figure 1. Examination of the individual results shows that in no instance did 2 Gm. of Benemid, administered as 0.5 Gm. every six hours for twenty-four hours prior to the administration of 4 Gm. of sodium PAS, fail to produce an increase of the plasma concentrations of PAS over those obtained when the same dose of sodium PAS was administered alone. It is of interest to observe that a single oral 2 Gm. dose of Benemid in 4 subjects (J. C., F. M., C. S., and F. L.) had an enhancing effect on PAS plasma concentrations which was definite but less striking than that obtained when the same total amount of Benemid was administered in divided doses over a twenty-four hour period. In one patient (H. J.) the single 2 Gm. dose had an effect almost equal to that of 2 Gm. when administered as 0.5 Gm. every six hours, but in patients P.S. and J.M., a single 2 Gm. dose of

Benemid had little effect. The average results in the 7 patients are presented in the right lower corner of figure 1, and the actual values graphed are presented in table 1.

The mean plasma concentrations of PAS[3] for the three periods of the study were: 1.00 mg. per 100 ml. (no Benemid), 1.71 mg. per 100 ml. (single dose of Benemid), and 2.63 mg. per 100 mg. (Benemid in divided doses). The means were determined with a standard error of ± 0.20 mg. per 100 ml., and the 95 per cent confidence limits are ± 0.44 mg. per 100 ml. Thus, a single dose of Benemid gave significantly greater plasma concentrations of PAS than when Benemid was not administered (P = 0.05), and divided doses of Benemid gave plasma concentrations of PAS highly significantly greater than when the same total amount of drug was given at one time (P = 0.01).

TABLE 1

BENEMID AND PAS

PAS Plasma Concentrations Modified by Benemid

(Averages of the same 7 patients)

PAS* SINGLE DOSE, ORALLY	BENEMID (ORALLY)	PAS PLASMA CONCENTRATIONS (MG. PER 100 ML.) HOURS AFTER PAS				
		½	2	4	6	8
4 Gm.	—	9.45	8.12	2.25	0.56	0.19
4 Gm.	2 Gm.** (Single dose)	7.90	9.02	2.97	1.02	0.39
4 Gm.	0.5 Gm.† (Every 6 hrs. X6)	9.69	11.56	5.26	1.82	0.82

* PAS was administered as the sodium salt.

** Administered 1 hour prior to administration of PAS.

† Doses given for 24 hours before PAS and during sampling.

DISCUSSION

The value of PAS in the therapy of human tuberculosis has been established in a number of studies, including several with the use of untreated controls (9, 10). In a recent review (11), Bogen calls attention to the confusion which existed in the early literature with regard to the physical properties of the PAS preparations which had been employed. It is undoubtedly true that much of the excessive nausea and vomiting which was originally reported was due to the administration of PAS in the form of its hydrochloride which is very acidic. When PAS is administered in the form of the free acid it is less irritating than when the hydrochloride is given, but nausea and vomiting are frequent when daily doses in excess of 8 and 12 Gm. are administered, and only an occasional patient is able to tolerate 16 Gm. of free acid. The sodium salt of PAS employed in this investigation was prepared immediately prior to oral administration by the use of effervescent tablets[4], each containing 1 Gm. of PAS and a sufficient

[3] The plasma concentrations of PAS at one-half hour and two hours have been eliminated from the statistical analysis for the reason that these samples were drawn during the period required for PAS from a single oral dose to be absorbed and distributed in the body fluids.

[4] The authors are indebted to Sharp and Dohme, Inc. for Proposa effervescent tablets of para-aminosalicylic acid and for the Benemid used in this study.

quantity of sodium bicarbonate to convert the acid to the sodium salt within a matter of minutes when the tablets were dropped into 15 to 30 ml. of water. The clear or slightly amber solution which results from the addition of 1 to 4 Gm. of PAS in the form of these effervescent tablets to 30 ml. of water has a saline taste but is well tolerated by patients. No gastrointestinal symptoms were observed following the use of single 4 Gm. doses of sodium PAS during these studies.

To date there has been no correlation between therapeutic effectiveness and the plasma concentrations of PAS which are attained. *In vitro* studies of the sensitivity of various strains of *M. tuberculosis* to PAS have demonstrated that concentrations of 0.015 to 1.53 mg. per 100 ml. are sufficient to inhibit growth (12). Plasma concentrations of PAS in excess of these inhibitory concentrations are attained in human subjects when 12 Gm. or more of PAS are administered daily but not when 6 and 8 Gm. are administered. At best, plasma concentrations are only an indirect index of the concentration of PAS at the tissue sites of tuberculous involvement, but failure to maintain inhibitory plasma concentrations of PAS suggests that PAS is present at the actual sites of infection in even lower concentrations. It may be assumed that high plasma concentrations of PAS would establish diffusion gradients that would favor the attainment of bacteriostatic concentrations of PAS at the sites of tuberculous infection in a greater degree than lower plasma concentrations of PAS. Although there has been no demonstration of increased therapeutic effect with higher plasma concentrations of PAS, within limits this may be expected to hold true. Thus there are a number of advantages which might be gained from the use of Benemid: (a) an actual increase in therapeutic efficacy of PAS; (b) more convenient dosage schedules of PAS; and (c) a reduction of the incidence of the emergence of PAS- and streptomycin-resistant strains of *M. tuberculosis*.

The original concept of the action of carinamide was that of an inhibition of a specific enzymatic excretory transport system of the renal tubules (13). More recent work (1), however, indicates that carinamide acts upon an enzymatic conjugation system which is concerned with the conjugation of various compounds with glycine. It is of interest that Ragaz (6), acknowledging the fact that inhibition of tubular excretion might result in the elevation of the plasma concentration of a particular drug, suggested that a similar effect might be obtained if the metabolism of the particular substance were influenced in such manner as to present the drug to the renal tubules in a form which was less readily excreted. Thus, PAS as the free acid might be less well excreted by the renal tubules than some of its numerous conjugated forms that have been described (8). The evidence that both carinamide and Benemid act upon a conjugase system believed to be related in some manner to the reversible inhibition of para-aminohippurate (PAH), penicillin, and phenolsulphonphthalein (PSP) excretion (1) suggests that carinamide and Benemid inhibit the conjugation of PAS because PAS in unconjugated form is less readily excreted than in the conjugated form; both the inactivation and elimination of PAS are retarded.

The work here reported indicates that single 2 Gm. oral doses of Benemid increase by 1.6 to 2.1 times the plasma concentrations of PAS observed four to

eight hours after a single 4 Gm. oral dose of PAS. When a 2 Gm. dose of Benemid is administered as 0.5 Gm. every six hours for a period of twenty-four hours prior to the administration of a 4 Gm. dose of PAS, plasma concentrations of PAS are elevated by 2.3 to 4.1 times. The present indications are that a 2 Gm. per day dose of Benemid is equal to a 24 Gm. per day dose of carinamide with respect to enhancement effects on PAS (14).

SUMMARY

A new compound, *p*-(di-n-propylsulfamyl)-benzoic acid, Benemid, has been shown to increase the plasma concentrations of *p*-aminosalicylic acid (PAS). A single oral 2 Gm. dose of Benemid produced a 1.6- to 2.1-fold increase at four, six, and eight hours; and 2 Gm. of Benemid distributed over a twenty-four-hour period produced a 2.3- to 4.1-fold increase of PAS plasma concentrations at four, six, and eight hours after a single oral dose of 4 Gm. of PAS. It is suggested that Benemid inhibits an enzymatic system concerned with the inactivation of PAS by conjugation with glycine and, assuming that the unconjugated PAS is less rapidly eliminated, PAS is conserved within the body. Enhancement of PAS concentrations in the plasma by the use of Benemid may extend the usefulness of PAS in the treatment of tuberculosis by increasing the direct therapeutic effect of PAS and by facilitating the action of PAS in retarding the emergence of streptomycin-resistant strains of *M. tuberculosis*.

SUMARIO

Está demostrado que un nuevo compuesto, el ácido p-(di-n-propilsulfamil)-benzoico, Benemid, hace subir las concentraciones del ácido *p*-aminosalicílico (PAS) en el plasma sanguíneo. Una sola dosis oral de 2 Gm. de Benemid produjo un aumento de 1.6 a 2.1 a las cuatro, seis y ocho horas y 2 Gm. de Benemid, repartidos durante un período de veinticuatro horas, produjeron un aumento de 2.3 a 4.1 en las concentraciones de PAS en el plasma a las cuatro, seis y ocho horas de tomar una sola dosis oral de 4 Gm. de PAS. Parece que el Benemid inhibe un mecanismo enzimático que interviene en la inactivación del PAS por conjugación con la glicina y, asumiendo que el PAS no conjugado es eliminado con menos rapidez, consérvase así el PAS en el organismo. El aumento de las concentraciones de PAS en el plasma mediante el empleo de Benemid puede ampliar la utilidad del PAS en el tratamiento de la tuberculosis por acrecentar el efecto terapéutico directo del mismo y facilitar su acción retardadora sobre la aparición de cepas estreptomicinorresistentes del *M. tuberculosis*.

Acknowledgment

The authors wish to express their indebtedness to Drs. Charles A. Heiken, Peter A. Theodos, and J. Kirschner, Chiefs of Service of the Department of Chronic Diseases of the Chest, Philadelphia General Hospital, for the privilege of studying patients on their services; to Mrs. Alice E. Pitt for technical assistance, and to Mr. Joseph L. Ciminera, Biometrician, Medical Research Division of Sharp and Dohme, Inc., for statistical analysis of data.

REFERENCES

(1) Beyer, K. H.: Personal communication.
(2) Boger, W. P., Gallagher, M. E., and Pitts, F. W.: The effect of a new benzoic acid derivative on penicillin and para-aminosalicylic acid, J. Phila. Gen'l. Hosp., 1950, *1*, 51.
(3) Boger, W. P., and Baker, R. M.: A comparison of effect of carinamide and benzoic acid on penicillin plasma concentrations, Proc. Soc. Exper. Biol. & Med., 1947, *66*, 1.
(4) Boger, W. P., and Flippin, H. F.: Penicillin plasma concentrations: Increase and prolongation with carinamide and newer depot penicillin preparations, J. A. M. A., 1949, *139*, 1131.
(5) Seeler, A. O., Wilcox, C., Finland, M.: Enhancement of blood levels by carinamide during intramuscular administration of penicillin, J. Lab. & Clin. Med., 1947, *32*, 87.
(6) Ragaz, L.: Zur pharmakologie der p-aminosalicylsaure, Schweiz. med. Wchnschr., 1948, *78*, 1213.
(7) Horne, N. W., and Wilson, W. M.: Effect of carinamide on excretion of *p*-aminosalicylic acid, Lancet, 1949, *2*, 507.
(8) Way, E. L., Smith, P. K., Howie, D. L., Weiss, R., and Swanson, R.: The absorption, distribution, excretion and fate of para-aminosalicylic acid, J. Pharmacol. & Exper. Therap., 1948, *93*, 368.
(9) The Therapeutic Trials Committee of the Swedish National Association against Tuberculosis: Para-aminosalicylic acid treatment in pulmonary tuberculosis: Comparison between 94 treated and 82 untreated cases, Am. Rev. Tuberc., 1950, *61*, 597.
(10) Marc Daniels: Scientific appraisement of new drugs in tuberculosis (editorial), Am. Rev. Tuberc., 1950, *61*, 751.
(11) Bogen, E.: Para-aminosalicylic acid treatment of tuberculosis: A review, Am. Rev. Tuberc., 1950, *61*, 226.
(12) Sievers, O.: Experimental trials with PAS against various kinds of bacteria, Nord. med., 1947, *33*, 147.
(13) Beyer, K. H.: Concept of competitive inhibition of the renal tubular excretion of penicillin, Science, 1947, *105*, 94.
(14) Boger, W. P., Pitts, F. W., and Gallagher, M. E.: 'Benemid' and carinamide: Effect on para-aminosalicylic acid plasma concentrations compared (to be published).

TUBERCULOUS PATIENTS TWO AND A HALF YEARS AFTER STREPTOMYCIN TREATMENT[1]

M. MAXIM STEINBACH,[2] GEORGE C. LEINER, ABRAHAM A. POLACHEK AND PAUL HELLER

(Received for publication November 3, 1949)

There are many publications dealing with the results of streptomycin treatment in various forms of tuberculosis, but few (1) with the follow-up of these patients. It was thought it would be of interest, therefore, to report the present condition of the first 35 patients from this service who were treated with streptomycin and in whom treatment was terminated at least two and one-half years ago.

With very few exceptions, the patients selected during this early phase of treatment with streptomycin had tuberculous lesions which were not expected to be controlled by the other methods available. There were 13 males and 22 females in the series. All had sputum positive for acid-fast bacilli on direct smear before treatment except one of the two with genitourinary involvement (both of whom had urine positive on direct smear for acid-fast bacilli). All of the patients were considered to have poor or hopeless prognoses. It may be of some interest to mention that two patients with idiopathic epilepsy and one with otosclerosis were treated and showed no untoward effects.

Classification: For purposes of analysis, the patients were classified into the four following groups, according to the clinical form of their disease:

Group I: 24 with recent, active progressive pulmonary disease moderately or far advanced
Group II: 4 with fibrocavitary, far advanced pulmonary disease
Group III: 5 with laryngeal or endobronchial disease
Group IV: 2 patients with residual, genitourinary tuberculosis, following nephrectomy.

Regimens: Patients in groups I, II, and IV received 2 Gm. of streptomycin per day intramuscularly in eight divided doses, except 2 who received 1 Gm. per day, and 2 who received 3 Gm. per day. Those in group III received 0.5 Gm. per day in five divided doses by inhalation. All organisms were sensitive to fractions of a microgram of streptomycin per cc. in Dubos medium before therapy, but after six to eight weeks of treatment the organisms became resistant even to high concentrations of streptomycin (100 γ) in most of the cases.

RESULTS

Group I (See tables 1A and 1B): The 24 patients in Group I (active, progressive disease) consisted of 6 males and 18 females, ranging in age from 17 to 50. All were observed from six to twenty-four months prior to treatment, and each had a

[1] From the Pulmonary Division, Montefiore Hospital, Bronx, New York, and Country Sanatorium, Bedford Hills, New York.

[2] Deceased.

progressively downward course. They were treated for an average of 93 days with an average of 190 Gm. of streptomycin. Seventeen patients had one continuous course, whereas 8 received a second course of streptomycin. Three of

TABLE 1A

Exudative Tuberculosis

(Group I)—Clinical Results

	NUMBER	AT END OF STREPTOMYCIN		AT PRESENT			
		Improved	Unimproved	Arrested	Quiescent	Active	Ceased
1. Streptomycin and bed rest	13	13	0	7	1	4	1
2. Streptomycin, bed rest, and pneumothorax	3	3	0	2	1		
3. Streptomycin, bed rest, and thoracoplasty on same side	3	3	0	1	2		
4. Streptomycin, bed rest, and thoracoplasty on opposite side	4	4	0	4			
5. Streptomycin, bed rest, and cavernostomy	1	1	0		1		
Total	24	24	0	14	5	4	1

TABLE 1B

Exudative Tuberculosis

(Group I)—Sputum Results

	NUMBER	AT END OF STREPTOMYCIN			AT PRESENT		
		Negative culture	Negative Concentrate	Positive Smear or Concentrate	Negative Culture	Negative Concentrate	Positive Smear or Concentrate
1. Streptomycin and bed rest	13	8	3	2	6	3	4
2. Streptomycin, bed rest, and pneumothorax	3	0	1	2	2	1	
3. Streptomycin, bed rest, and thoracoplasty on same side	3	0	2	1	1		2
4. Streptomycin, bed rest, and thoracoplasty on opposite side	4	1	0	3	4		
5. Streptomycin, bed rest, and cavernostomy	1	0	0	1			1
Total	24	9	6	9	13	4	7

the latter group were re-treated principally because of reactivation of endobronchial lesions, one because of persistence of tubercle bacilli in the sputum, one because of a reappearance of tubercle bacilli in the sputum (although there was continued roentgenographic and clinical improvement), and the remaining 3 in order to prevent progression during thoracoplasty procedures.

Thirteen of these 24 patients received streptomycin plus bed rest alone. Of these, all showed clinical and roentgenographic improvement at the end of their course of treatment, although one of these began to show some progression just prior to termination of treatment. The sputum became negative for *M. tuberculosis* on culture in 8, negative on microscopic examinations in 3, and showed no change in the other two.

At the present time, after at least two and a half years since treatment was stopped, 7 are classified as arrested; one, quiescent; 4, active; and one has died. Six patients have sputum or gastric contents negative for tubercle bacilli on

TABLE 2A

Fibrocavitary Tuberculosis

(Group II)—Clinical Results

	NUMBER	AT END OF STREPTOMYCIN		AT PRESENT			
		Improved	Unimproved	Arrested	Quiescent	Active	Ceased
1. Streptomycin and bed rest	3	0	3	0	0	2	1
2. Streptomycin and thoracoplasty	1	1	0	1	0	0	0
Total	4	1	3	1	0	2	1

TABLE 2B

Fibrocavitary Tuberculosis

(Group II)—Sputum Results

	NUMBER	AT END OF STREPTOMYCIN			AT PRESENT		
		Negative Culture	Negative Concentrate	Positive Smear or Concentrate	Negative Culture	Negative Concentrate	Positive Smear or Concentrate
1. Streptomycin and bed rest	3	0	0	3	0	0	3
2. Streptomycin and thoracoplasty	1	0	0	1	1	0	0
Total	4	0	0	4	1	0	3

culture; 3, on microscopic examination. Four patients have sputum which is positive for acid-fast bacilli on smear or concentrate. During this period of over two and a half years one patient has died and 4 patients have shown definite relapses, with a return of positive sputum and progression of the lesions as viewed on the roentgenogram. Three patients have shown instability of pulmonary lesions, with a return of infectiousness. One of these developed a small cavity, and another a pleural effusion which has since resorbed. One had a relapse of his genitourinary condition, although the pulmonary lesion for which he was treated is arrested.

The other 11 cases of Group I had some complementary procedure, such as

pneumothorax, cavernostomy, or thoracoplasty, at the same time that the streptomycin was administered. At the end of streptomycin therapy they were all considered improved; infectiousness had been reversed in 4, while 7 continued to discharge tubercle bacilli. At the end of two and a half years, the disease is arrested in 7; quiescent in 4; 8 are no longer discharging tubercle bacilli; and 3 remain infectious. Three of these had a second course of streptomycin but just as a preventive measure during thoracoplasty. The course of 2 patients who received a thoracoplasty was reported in detail by Steinbach *et al.* (2).

TABLE 3A

Laryngeal or Endobronchial Tuberculosis

(Group III)—Clinical Results

	NUMBER	AT END OF STREPTOMYCIN		AT PRESENT	
		Improved	Unimproved	Arrested	Active
1. By inhalation and injection (laryngeal cases)	2	2	0	1	1
2. By inhalation	3	2	1	2	1
Total	5	4	1	3	2

TABLE 3B

Laryngeal or Endobronchial Tuberculosis

(Group III)—Sputum Results

	NUMBER	AT END OF STREPTOMYCIN			AT PRESENT		
		Negative Culture	Negative Concentrate	Positive Smear or Concentrate	Negative Culture	Negative Concentrate	Positive Smear or Concentrate
1. By inhalation and injection (laryngeal cases)	2	0	1	1	1	0	1
2. By inhalation	3	1	1	1	2	0	1
Total	5	1	2	2	3	0	2

Thus in Group I, at the end of two and a half years' follow-up, the lesions are arrested in 14 of 24 patients, quiescent in 5, active in 4, and one patient has died. The sputum has been converted from "positive" on direct smear to "negative" on culture in 13 patients and to "negative" on concentrate in 4 more. Seven of the original 24 have remained infectious. Of interest is the fact that 3 patients showed incidental healing of rectal fistulas during the streptomycin treatment. Of the 3, one also closed a cavernostomy wound during the treatment.

Group II (See tables 2A and 2B): The 4 patients with fibrocavitary disease in this group consisted of 2 males and 2 females, ranging in age from 33 to 56 years. Each had a long history of tuberculosis of at least ten years' duration. Three

of these were treated because no other therapy was available, and the fourth received streptomycin during a thoracoplasty, in view of extensive disease and contralateral pneumothorax. These patients received an average of 93 Gm. of streptomycin in 56 days. No essential change was found during treatment in the first 3 patients; but, at the present time, one is dead and 2 have progressive disease. The fourth is now considered as arrested following thoracoplasty. These results are in agreement with those of other observers who found that streptomycin has no appreciable effect on this type of tuberculosis.

Group III (*See tables 3A and 3B*): The 5 patients with laryngeal or endobronchial disease in this group consisted of 3 males and 2 females, aged 32 to

TABLE 4A

Genitourinary Tuberculosis

(Group IV)—Clinical Results

	NUMBER	AT END OF STREPTOMYCIN		AT PRESENT		
		Improved	Unimproved	Arrested	Quiescent	Active
Streptomycin intramuscularly	2	1	1	1	0	1
Total	2	1	1	1	0	1

TABLE 4B

Genitourinary Tuberculosis

(Group IV)—Urine Results

	NUMBER	AT END OF STREPTOMYCIN			AT PRESENT		
		Negative Culture	Negative Concentrate	Positive Smear or Concentrate	Negative Culture	Negative Concentrate	Positive Smear or Concentrate
Streptomycin intramuscularly	2	0	1	1	1	0	1
Total	2	0	1	1	1	0	1

43 years. Three of these were treated by streptomycin aerosol alone, while 2 required a course of intramuscular injections because of severe asthmatic attacks caused by inhalation of streptomycin. Both of these had laryngeal disease, which precluded bronchoscopic examination. They showed marked improvement of the laryngeal lesions with intramuscular therapy. Of the 3 patients with endobronchial disease, treated by aerosol alone, 2 showed healing of the lesions at the end of treatment. One had sputum positive for tubercle bacilli at that time because of a small cavity which was subsequently collapsed by pneumothorax, followed by "conversion" of sputum. The pneumothorax was made possible by healing of the endobronchial disease following streptomycin therapy. Of the 5 patients, the lesions of 3 are now healed, with cultures negative for tubercle bacilli; and in 2 the disease is still active and they remain infectious.

Group IV (*See tables 4A and 4B*): This last group consisted of 2 patients, both males, 33 and 38, respectively, who had nephrectomies for tuberculosis of the kidney two to three years prior to treatment with streptomcyin for residual genitourinary tuberculosis and active pulmonary lesions. They received an average of 167 Gm. of streptomycin for 84 days. At the end of therapy both showed improvement as far as their pulmonary condition was concerned, but in only one of these had genitourinary improvement occurred with a "negative" urine concentrate. In the other patient progression of a tuberculous cystitis occurred and the urine smears continued to be positive for acid-fast bacilli. The pulmonary disease of both patients is now arrested, but only the former has a "negative" urine.

SUMMARY

1. Of 24 patients with recent, active, progressive pulmonary disease, all showed immediate improvement with streptomycin. After two and a half years, the lesions are arrested in 14; quiescent in 5; active in 4; and one patient has died. During the interval, 4 patients had relapses of their pulmonary condition, 3 had instability of their pulmonary lesions, and one had progression of his genitourinary tuberculosis.

2. In 4 patients with fibrocavitary disease, streptomycin therapy did not appear to have any appreciable effect. After two and a half years, the disease is arrested in one, active in two, and was fatal in one.

3. Of 5 patients in the group with laryngeal or endobronchial tuberculosis, the lesions are healed in 3, while they remain unimproved in 2 of them.

4. Of 2 patients with residual genitourinary tuberculosis after nephrectomy, one has healed disease, while the pulmonary disease of both is arrested.

5. Of the entire group of 35 patients treated with streptomycin more than two and half years ago, the disease is at present arrested in 19; quiescent in 5; active in 9; and has been fatal in 2 instances.

SUMARIO

Los Tuberculosos a los Dos Años y Medio de la Estreptomicinoterapia

1. De 24 tuberculosos con reciente afección pulmonar evolutiva, activa, todos revelaron mejoría inmediata con la estreptomicina. Al cabo de dos años y medio, 14 están estacionados, 5 quiescentes, 4 activos y uno ha muerto. Durante ese intervalo, 4 tuvieron recidivas de su estado pulmonar, 3 mostraron inestabilidad de sus lesiones pulmonares y en uno se agravó su tuberculosis urogenital.

2. En 4 enfermos con afección fibrocavitaria, la estreptomicinoterapia no pareció ejercer efecto apreciable. Al cabo de dos años y medio, uno se halla estacionado, 2 están activos y uno ha muerto.

3. De 5 pacientes del grupo con tuberculosis laríngea o endobronquial, 3 han cicatrizado, en tanto que 2 permanecen sin mejoría.

4. De 2 enfermos con tuberculosis genitourinaria residual postnefrectómica, uno ha cicatrizado, en tanto que la afección pulmonar se halla estacionada en ambos.

5. De todo el grupo de 35 enfermos tratados con la estreptomicina hace más de dos años y medio, 19 se hallan actualmente estacionados, 5, quiescentes, 9, activos, y 2 han muerto.

REFERENCES

(1) Olsen, A. M., and Hinshaw, H. C.: Tuberculosis of the trachea and major bronchi: Results of treatment with streptomycin, Am. Rev. Tubere., 1949, *60*, 32.

(2) Steinbach, M. M., Leiner, G. C., Polachek, A. A., and Heller, P.: Streptomycin and thoracoplasty, Am. Rev. Tubere., 1948, *57*, 593.

AUREOMYCIN IN THE TREATMENT OF TUBERCULOSIS[1,2]

W. S. SCHWARTZ, S. T. WALTON, AND R. E. MOYER

(Received for publication October 14, 1949)

Since aureomycin has been found to be effective against infections caused by a large variety of bacteria, certain *Rickettsiae*, and some of the viruses and, because of the need for an additional antibiotic to help combat infections caused by the tubercle bacillus, it was decided that a clinical trial of the drug was indicated. Some reports have indicated that aureomycin has had little effect against tuberculosis in guinea pigs (1), mice (2), and humans (3, 4). One patient suffering from tuberculous adenitis with multiple draining sinuses was reported as having been benefited (5).

While aureomycin has been found to be too unstable to permit satisfactory determination of its degree of effectiveness against tubercle bacilli *in vitro* when serum is also present, the use of special media has made possible the demonstration that concentrations of as little as 2.5 to 4.55 γ per cc. can be effective against the strain H37Rv in the absence of serum (1, 2). The range of these concentrations is at least within the range of blood levels of the drug found during the treatment of patients.

OBSERVATIONS

Clinical material: Beginning May 10, 1949, 10 patients were given 3 Gm. of aureomycin[3] daily by mouth for thirty days. Two 250 mg. capsules were swallowed every three hours from 6:00 a.m. to 9:00 p.m., with the aid of a few ounces of milk. All of the patients had received a course of streptomycin at some time previously. In all but one of the cases, tubercle bacilli were presumed to be resistant to streptomycin on the basis of isolation of cultures of resistant strains, lack of clinical effect on the the lesion, or both. In all other respects the patients would have been considered to be suitable for treatment with streptomycin.

Concentrations of aureomycin in the blood: At ten o'clock in the morning on the first day of treatment, one hour after the second dose, blood was withdrawn from each patient and tested for its aureomycin content by the method of Dornbush and Pelcak (6), using the Lederle *B. cereus* No. 5 as the test organism. The preparation of the test was completed by noon and the results were read by four o'clock in the afternoon of the same day. As little as 0.05 γ per cc. of the drug was detectable by the method employed. In two or three specimens a trace of aureomycin was found but the others showed none at all.

---

[1] From the Department of Medicine and Surgery, Veterans Administration, Oteen, North Carolina.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. Statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[3] The aureomycin hydrochloride was supplied through the courtesy of the Lederle Laboratories, Pearl River, N. Y.

After the first day of therapy, appreciable serum levels were attained and maintained throughout the period of treatment (table 1). Determinations were made twice weekly during the four weeks. Tests performed on all patients twelve hours after the last dose of aureomycin showed a minimum drug content of 1.6 γ per cc. and a maximum of 6.4. Thus, at this time, an appreciable serum level was maintained without drug administration for at least twelve hours.

Blood specimens collected at 3:00 p.m., obviously had a three-, six-, and nine-hour interval since the last dose of aureomycin, but evidence of cumulative

TABLE 1

Aureomycin Blood and Urine Levels (γ per cc.) after Treatment Established for at Least Several Days

CASE	SAMPLE TAKEN AT 3:00 P.M.		12 HOURS AFTER LAST DOSE	URINE
	Maximum	Minimum		
1. B. W.	3.2	1.6	3.2	200
2. C. P.	6.4	3.2	3.2	100
3. C. W.	3.2	0.4	3.2	200
4. E. B.	6.4	1.6	3.2	200
5. A. F.	12.8	0.2	3.2	400
6. J. P.	6.4	—	1.6	1,600
7. N. H.	3.2	1.6	1.6	100
8. W. D.	3.2	1.6	1.6	400
9. J. C.	6.4	0.4	6.4	100
10. W. R.	12.8	12.8	6.4	1,600

effect was not seen in all cases. Lepper and co-workers (7) found peak levels at three and six hours after the last dose.

There appeared to be no difference in serum aureomycin concentration when the test was set up immediately after the collection of the samples (within two hours), or when the serum was separated quickly and stored at 0°C. until the next day. Comparative aureomycin controls were run with freshly prepared solutions and with solutions stored in concentrated form, i.e., 2,500 γ per cc. for two weeks at 0°C. and pH 4.8. No diminution of potency of the drug was detectable under these conditions. Two specimens were divided and tests run simultaneously on serum and citrated plasma. A reduction in drug content of one-fourth to one-half was observed in the citrated portion, although an aureomycin control series to which a comparable quantity of citrate was added appeared unaffected. The citrate may have had some mordant effect on the plasma-drug mixture which "fixed" or "inactivated" a portion of the aureomycin.

After nine days of therapy, the urine content of aureomycin was determined. Specimens were collected at 10:00 a.m. Levels ranged from 100 to 1,600 γ per cc. of urine. These values were higher than those previously reported by Paine and associates (8) who used a lower dosage of 1 to 2 Gm. daily.

Toxicity: Nine of the patients experienced nausea. Five of these vomited occasionally and 4 had diarrhea. One patient remained unaffected. There was a tendency for these symptoms to diminish as the treatment continued and to disappear in most instances within one to two weeks. A complete blood count, urinalysis, and determination of blood urea nitrogen was done before, and every

two weeks during, treatment. A blood sedimentation rate, audiogram, and caloric test of vestibular function was done before and after treatment. No changes indicative of toxicity were revealed in 9 of the cases. In one (B. W.) albumin and many casts appeared in the urine.

Although the patients had had streptomycin therapy previously, all had normal audiograms and caloric tests both before and after receiving aureomycin.

REPORT OF CASES

Three patients were treated primarily for pulmonary tuberculosis, 5 for persistent tuberculous sinuses, and 2 for tuberculous laryngitis.

Case 1. B. W., a 58-year-old Negro male, was admitted December 12, 1947, suffering from moderately advanced pulmonary tuberculosis. His sputum was positive for tubercle bacilli on many examinations. Streptomycin, 1 Gm. daily, was given from May 19 to June 29, 1948, and again from October 6 to October 27, 1948, because of exacerbations of pulmonary disease. Tubercle bacilli isolated from the sputum on September 15, 1948 were found to grow in a concentration of 100 γ per cc. of streptomycin. Roentgenograms obtained on April 4 and May 6 showed steadily progressive disease in the right lung when compared with a film taken on February 1, 1949. Treatment with aureomycin was begun on May 10, 1949. Films taken on May 23 and June 8 showed moderate clearing of the fresh disease on the right. This patient suffered from nausea and diarrhea during the first week of treatment, but did not vomit. The nausea continued to a lessened degree during the second week, following which there were no symptoms of toxicity. His general feeling of well being was improved. After treatment was completed his pulmonary symptoms increased and a roentgenogram taken on July 6 showed a marked increase of shadows throughout the right lung. He died on July 8, 1949.

Case 2. C. P., a 30-year-old white male was admitted May 1, 1948, suffering from far advanced pulmonary tuberculosis. His sputum was found to be positive for tubercle bacilli on many examinations. He had received one Gm. of streptomycin daily from May 10 to June 21, 1948 because of progressive pulmonary disease. Tubercle bacilli isolated from the sputum on June 21, 1948 were found to grow in a concentration of 100 γ per cc. of streptomycin. Serial roentgenograms from December 29, 1948 to May 6, 1949 showed gradually increasing disease in the right lung. Aureomycin was begun on May 10, 1949. Roentgenograms obtained on May 26 and June 8, 1949 showed no change when compared with the one taken before treatment. This patient suffered no toxic symptoms until the last two weeks of treatment, during which time he had nausea and vomiting, but no diarrhea. His general feeling of well being was improved. There has been practically no change in his general condition or in the appearance of his chest films since treatment was completed.

Case 3. C. W., A 26-year-old white male was admitted October 29, 1948, suffering from far advanced pulmonary tuberculosis. His sputum was positive for tubercle bacilli on many examinations. He received 1 Gm. of streptomycin daily from November 11 to December 22, 1948 because of tuberculous laryngitis. This improved considerably under treatment. He received 2 Gm. of dihydrostreptomycin every third day from April 10 to May 1, 1949 because of an exacerbation of pulmonary disease. Tubercle bacilli isolated from the sputum on March 14, 1949 were found to grow in a concentration of 100 γ per cc. of dihydrostreptomycin. Serial roentgenograms of the chest taken on April 4, May 3, and May 11, 1949 showed gradually increasing disease in the upper third of the left lung. Aureomycin was begun on May 11, 1949. Subsequent roentgenograms obtained during treatment on May 20 and June 1, as well as following treatment on June 17 and August 27, showed no change in either lung. No toxic symptoms were experienced by this patient and his general feeling of well being was improved.

The following 5 patients were treated primarily because of the presence of persistent tuberculous sinuses.

Case 4. E. B., a 24-year-old Negro male, was admitted June 26, 1947, suffering from minimal pulmonary tuberculosis and multiple tuberculous bone lesions, complicated by draining sinuses. He received 1 Gm. of streptomycin daily from September 5 to December 5, 1947 and again from August 14 to September 24, 1948. Considerable improvement was noted after these courses of treatment, but the sinuses recurred. He received 2 Gm. of dihydrostreptomycin daily from January 8 to February 19, 1949 without any clinical effect. Studies of the degree of resistance of this patient's tubercle bacilli to streptomycin were lacking. At the time treatment with aureomycin was begun on May 10, 1949, there were rather extensive sinuses originating in lesions of the right elbow and right foot. No improvement in the appearance of the sinuses was noted during treatment. He suffered some nausea and vomiting on the first day and had some diarrhea during the first few days of treatment, but had no toxic symptoms thereafter. His general feeling of well being was improved.

Case 5. A. F., a 52-year-old Negro male, was admitted April 15, 1947, suffering from moderately advanced pulmonary tuberculosis and tuberculosis of the spine. The latter was involved from the third lumbar to the third sacral vertebra, and there was a tuberculous sinus in this region. His sputum was negative for tubercle bacilli. Streptomycin, 1 Gm. daily, was given from September 15, 1947 to February 21, 1948 and again from December 11, 1948 to January 22, 1949. A spinal fusion was done on November 19, 1948, and a persistent sinus failed to heal during, or following, the second course of streptomycin. By the time aureomycin treatment was commenced on May 10, the sinus had grown somewhat smaller and did not seem to extend deeply into the tissues. During treatment with aureomycin the sinus continued its tendency to heal, and epithelization took place before the treatment was finished. Interestingly enough, this patient suffered from nausea and vomiting occasionally before treatment with aureomycin and this improved during treatment. He had no diarrhea. His general feeling of well being was improved.

Case 6. J. P., a 28-year-old Negro male, was admitted February 24, 1949, suffering from tuberculous involvement of the spine, extending through the first and second lumbar vertebrae. This was complicated by a draining sinus. There was no evidence of pulmonary tuberculosis. He had received two courses of streptomycin before admission to the hospital, but the dosage and duration of treatment were unknown. Moderate clinical improvement occurred during the first course, but none was seen during the second. The sinus remained essentially unchanged until aureomycin treatment was begun on May 10. During treatment it was noted that drainage decreased to some extent, but there was no evidence of healing. This patient suffered from nausea and vomiting during the first two weeks of treatment and diarrhea the first two days. Following this there were no toxic symptoms. His general feeling of well being was improved.

Case 7. N. H., a 29-year-old Negro male, was admitted October 23, 1947, suffering from tuberculous involvement of the spine, extending through the second and third lumbar vertebrae. There was a draining sinus in this area. There was no evidence of pulmonary tuberculosis. Streptomycin, 0.2 Gm., was given daily from November 21, 1947 to April 3, 1948. The sinus healed. Subsequent to this he developed evidence of tuberculosis of the left knee joint and an arthrodesis was done July 12, 1948. One gram of streptomycin was given daily from July 12 to August 2, 1948. The operative incision healed promptly. He developed a large cold abscess in the lumbar region in the fall of 1948. This was incised and drained on November 22, 1948. There was still a large sinus tract remaining from the abscess in the lumbar region when treatment with aureomycin was begun on May 10, 1949. There was no change in the amount of drainage or other sign of healing during treatment. The only evidence of toxicity consisted of slight nausea. The patient's general feeling of well being improved. He was then given a third course of streptomycin, and the sinus healed.

Case 8. W. D., a 29-year-old Negro male, was admitted January 4, 1945. He was found to have minimal pulmonary tuberculosis. He also suffered from multiple tuberculous lesions of the ribs and tuberculosis of the ninth dorsal and third lumbar vertebrae. There were tuberculous sinuses originating in all of these foci. Cultures demonstrated the presence of tubercle bacilli in the drainage. He was given two courses of 2 Gm. of streptomycin daily from July 1 to November 27, 1946 and from January 27 to May 27, 1947. Considerable improvement occurred and he was discharged from the hospital (July 14, 1948) as having attained maximum hospital benefit, with all sinuses healed. He was readmitted on March 25, 1949 and was found to have draining tuberculous sinuses below the left knee and in the left groin. Up to the time that aureomycin was begun on May 10, the sinus in the groin showed little change but those below the left knee were improving. During and following aureomycin treatment the sinuses below the knee closed. Drainage decreased from the sinus in the left groin, and pain and swelling disappeared, but there was no change in its size. This patient suffered from nausea and vomiting in the afternoon during the first two weeks of treatment. He had watery stools as long as aureomycin was given. In spite of this he thought that his general feeling of well being was improved.

The following 2 patients were treated primarily for tuberculous laryngitis.

Case 9. J. C., a 49-year-old Negro male, was admitted December 24, 1947. He was found to be suffering from far advanced pulmonary tuberculosis and tuberculous lymphadenitis. His sputum was found to be positive for tubercle bacilli. He was given 1 Gm. of streptomycin daily from January 19 to April 5, 1948. He became hoarse during the latter part of the course of streptomycin and a diagnosis of tuberculous laryngitis was made on April 16, 1948. It was supposed that this patient's tubercle bacilli had become resistant to streptomycin, but this was not confirmed until March 10, 1949, when they were found to grow in 100 γ per cc. of streptomycin. The laryngitis gradually grew worse and by the time aureomycin was begun on May 10, 1949, the patient was very hoarse and suffered considerable dysphagia. During treatment with aureomycin the dysphagia improved to some extent, but there was no change in hoarseness or in the appearance of the larynx. He complained of moderate nausea during treatment, but had no vomiting or diarrhea and thought that his general feeling of well being was improved.

Case 10. W. R., a 49-year-old white male, admitted January 19, 1949, was found to be suffering from far advanced pulmonary tuberculosis and tuberculous laryngitis. His sputum was positive for tubercle bacilli. He was given streptomycin, 1 Gm. daily, from February 6 to March 20, 1949. The larynx showed only moderate improvement after treatment was ended. After a few weeks of treatment tubercle bacilli isolated from the sputum were found to grow in a concentration of 100 γ per cc. of streptomycin. The appearance of the larynx remained about the same until aureomycin was begun on May 10, 1949, and still showed no change following treatment with this drug. The patient suffered mild nausea during the first week of aureomycin but had no evidence of toxic symptoms thereafter. His general feeling of well being was improved.

DISCUSSION

The results of treatment indicated that aureomycin exercised no specific effect on the tuberculous lesions of these patients. While improvement in the appearance of some of the draining sinuses occurred, it was thought to be due to the removal of some of the secondary infection, since the gain did not seem to be any more than may be encountered with the use of penicillin. In no instance was the speed or degree of healing comparable to what it has become customary to expect from streptomycin in like cases when the tubercle bacilli are still sensitive to the drug. It was believed that the symptomatic improvement noted in one

of the patients with laryngeal lesions could be explained on the same basis. The partial clearing of the pulmonary lesion in one case was thought to be due to chance. The patients in this series had little hope of returning to health at any time in the near future. While care was taken not to indicate that aureomycin was expected to effect a cure, it soon became evident to the patients that it was a powerful medicine of some kind, if only from its unpleasant effect on the gastrointestinal tract. This, plus the interest in the progress of the lesions shown by the doctors concerned, could not help but produce a certain amount of psychologic effect. Accordingly, it was believed that the improved feeling of well being experienced by the patients was due to a renewed hope of an early recovery.

SUMMARY

Three patients with pulmonary tuberculosis, 5 with tuberculous sinuses, and 2 with tuberculous laryngitis were given 3 Gm. of aureomycin daily by mouth for thirty days. Determinations of the concentrations of aureomycin attained in the blood during treatment showed that there was satisfactory absorption of the drug. Nevertheless, the results indicated that aureomycin is of no value in the treatment of tuberculosis.

SUMARIO

La Aureomicina en el Tratamiento de la Tuberculosis

Tres enfermos que padecían de tuberculosis pulmonar, 5 de fístulas tuberculosas y 2 de laringitis tuberculosa recibieron tres gramos diarios de aureomicina por vía bucal durante treinta días. Si bien los niveles sanguíneos observados durante el tratamiento revelaron absorción satisfactoria, el resultado indicó que la droga no es de valor en el tratamiento de la tuberculosis.

REFERENCES

(1) Steenken, W., Jr., and Wolinsky, E.: Tuberculostatic activity of aureomycin *in vitro* and *in vivo* (letters to the editors), Am. Rev. Tuberc., 1949, *59*, 221.

(2) Rake, G., and Donovick, R.: Tuberculostatic activity of aureomycin *in vitro* and *in vivo*, (letters to the editors), Am. Rev. Tuberc., 1949, *60*, 143.

(3) Yeager, R. L.: Personal communication.

(4) Steinbach, M. M., Dooneief, A. S., and Buchburg, A. S.: The use of aureomycin in pulmonary tuberculosis, Am. Rev. Tuberc., 1949, *59*, 624.

(5) Schoenbach, E. M., Bryer, M. S., and Long, P. H.: Pharmacology and clinical trial of aureomycin: A preliminary report, Ann. New York Acad. Sc., 1948, *51*, 267.

(6) Dornbush, A. C., and Pelcak, E. J.: The determination of aureomycin in serum and other body fluids, Ann. New York Acad. Sc., 1948, *51*, 218.

(7) Lepper, M. H., Dowling, H. F., Brickhouse, R. L., and Caldwell, E. R.: Blood and cerebral spinal fluid concentration of aureomycin after oral and intramuscular administration, J. Lab. & Clin. Med., 1949, *34*, 366.

(8) Paine, T. J., Jr., Collins, H. S., and Finland, M.: Laboratory studies with aureomycin, Ann. New York Acad. Sc., 1948, *51*, 228.

Case Reports

TUBERCULOUS INFECTION WITH STREPTOMYCIN-RESISTANT ORGANISMS[1,2]

L. S. ARANY AND W. G. LEWIS

(Received for publication October 19, 1949)

Attention has already been called to the possible public health hazard of streptomycin treatment of pulmonary tuberculosis (1, 2). Contacts of patients whose organisms developed resistance to streptomycin are potentially endangered because, if they contract the disease from these patients, their tuberculosis cannot be successfully treated with streptomycin if such treatment would otherwise be indicated.

In spite of considerable interest in this problem, only 2 cases of such infection with streptomycin-resistant organisms have been described so far (3, 4). Recently, a similar case was encountered at the Veterans Administration Hospital, Walla Walla, Washington.

A. A., a 22-year-old white male was employed here as a hospital attendant in January 1948. At that time, the Mantoux test with both first and second strength PPD was negative, and the chest roentgenogram was entirely normal. He was working on two wards, on both of which, almost exclusively, far advanced cases of pulmonary tuberculosis were treated. Approximately half of these patients were undergoing streptomycin treatment or had completed a course some time before. Among the latter, at least in sixteen cases, development of resistance to streptomycin was found to have occurred during the period of this man's employment. He resigned after four months' service and worked for a line crew, digging pole holes from May to August 1948. In the first few days of August 1948, he developed pain in the right chest, chills, and remittent type of fever up to 104°F. After hospitalization for three weeks in another institution, where the diagnosis of right pleural effusion was made and three aspirations performed, he was admitted on August 21, 1948. High temperatures continued for four more weeks, followed by a period of marginal fever. Aspirations were continued, but the lung failed to re-expand until decortication, performed on January 14, 1949, resulted in obliteration of the air space. The Mantoux test on admission was positive. Both the pleural fluid, which was always thin and clear, and the sputum were persistently negative for *M. tuberculosis* on smear and culture. A biopsy specimen from the peeled-off pleura revealed typical tuberculous tissue with caseation, but organisms could not be isolated from this specimen either. The only positive findings were the cultures of two urine specimens of January 8 and January 9, 1949, respectively, which showed heavy growth. The colonies so obtained were also inoculated into a guinea pig with positive results. Sensitivity tests on the organisms grown on either of these two cultures were made, and revealed that they were resistant to more than 100 γ of streptomycin both on solid and liquid media. Although the patient received streptomycin for three weeks prior to, and following, decortication (21 Gm. altogether), the urine specimens were cultured prior to this treatment. Cystoscopy, intravenous and retrograde pyelography showed no evidence of tuberculosis of the urinary tract; the urine sediment, which in three instances contained pus, was clear on subsequent examinations. On March 10, 1949 the urologist submitted the following report:

[1] From the Veterans Administration Hospital, Walla Walla, Washington.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. Statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

"Both lobes of the prostate are indurated. The induration is more marked on the left side. The right seminal vesicle is not palpable; the left is palpable and slightly tender, thickened, and does not discharge its contents on massage. No prostatic secretion obtained for microscopic study. Diagnosis: Tuberculous prostatitis?" On May 10, 1949 both lung fields were still clear on roentgenography; there was hardly any expectoration, and the sputum remained negative for *M. tuberculosis*. On June 27, 1949 the patient left the hospital against medical advice. He stayed at home, and followed a fairly strict bed rest regimen. At first, his course remained static, but in September 1949 his illness progressed rapidly. His private physician suspected brucellosis and treated him with aureomycin. On October 3, 1949 he was readmitted in a completely emaciated condition. A roentgenogram of the chest showed caseous nodular and caseous pneumonic lesions scattered diffusely throughout both lung fields; he also had tuberculous epididymitis and orchitis with hydrocele on the left. The sputum was positive for tubercle bacilli. Streptomycin, Gm. daily, was started on October 5, 1949, with no clinical response, and the patient died on October 10, 1949. Tubercle bacilli obtained from the sputum showed 100 per cent growth in a medium containing 100 γ of streptomycin per cc. The same high resistance was shown by tubercle bacilli obtained from fresh autopsy material (lungs). Autopsy revealed, in addition to the caseous pneumonic and nodular tuberculosis which involved the entire parenchyma of both lungs, an extensive hematogenous spread to the intestines, appendix, adrenal glands, prostate, testicles, seminal vesicles, and epididymides. (All laboratory examinations were carried out by Dr. E. L. Foote, pathologist, and Mr. B. H. Johnson, bacteriologist, of this hospital. One of the above-mentioned urine cultures was forwarded to Dr. Martin M. Cummings, director, Tuberculosis Evaluation Laboratory, P.H.S., Atlanta, Georgia, who confirmed the finding of resistance more than 100 γ.)

COMMENT

This is a case of an initially "tuberculin-negative" young man, who, after contact with streptomycin-treated tuberculous patients, developed tuberculous pleurisy. This condition usually follows primary infection within three to ten months. At the same time tubercle bacilli were recovered from his urine presumably because of the presence of tuberculous prostatitis, and these microorganisms showed an initial resistance to streptomycin of more than 100 γ.

Since streptomycin has been used quite extensively for the past two to three years, it is rather surprising that not more than three cases of infection with streptomycin-resistant organisms have thus far been reported. This may be due to the fact that streptomycin sensitivity tests have not yet been done on a large scale. Furtos mentions that among her patients, in 385 cases, no instance of initially high bacterial resistance was encountered, and our hospital staff has had the same experience. This again proves the insignificant role which superinfection plays in tuberculosis, a fact which has rather general acceptance among phthisiologists.

For proper evaluation of the actual hazard of streptomycin treatment to public health, streptomycin sensitivity tests should be made on all newly discovered cases of tuberculosis in every hospital which is equipped for this type of examination.

REFERENCES

(1) Oatway, W. H., Jr.: A streptomycin hazard to public health, J. A. M. A., 1948, *136*, 490.

(2) Shamaskin, A.: Comments on bacterial resistance to streptomycin, Dis. of Chest, 1949, *15*, 303.

(3) Furtos, N. C., and Doane, E. A.: Transmission of streptomycin-resistant tubercle bacilli in man, J. A. M. A., 1949, *140*, 1274.

(4) Brennan, A. J., and Wichelhausen, R. H.: Streptomycin-resistant tubercle bacilli, J. A. M. A., 1949, *140*, 1275.

SPONTANEOUS MEDIASTINAL EMPHYSEMA AND BILATERAL SPONTANEOUS PNEUMOTHORACES[1,2]

BERNARD HYDE AND LEROY HYDE

(Received for publication November 14, 1949)

There have been excellent reports on spontaneous mediastinal emphysema and spontaneous pneumothorax recently (1, 2), and very little can be added to these. The present case report is of a patient with spontaneous mediastinal emphysema and bilateral spontaneous pneumothoraces, an occurrence which must be very rare.

CASE REPORT

W. L. R., a 21-year-old white male was admitted to the hospital on November 29, 1948. He stated that he had been perfectly well until two days preceding admission, when, while sitting quietly eating lunch, he was seized with a sudden right upper chest pain. This pain was aggravated by deep breathing or by lying on his side or back. At the same time he noted some bubbling noises over his upper mediastinum beneath his sternum. He denied dyspnea, cyanosis, cough, sputum, fever, chills, weight loss, or other symptoms. His past history was interesting in that he described three previous episodes of sudden chest pain of similar character. The first occurred at the age of 17 on the left side, the second at the age of 18 on the right side, and the third, on the left side, three months prior to the present episode. In none of these three previous episodes were roentgenograms obtained. The chest pain in each instance disappeared within several days.

Family history revealed that the father has pulmonary tuberculosis and is hospitalized at present. The patient had a routine chest roentgenogram (figure 1) in September 1948, two months prior to admission, and this was negative.

On admission to the hospital the temperature was 99.8°F., the pulse rate was 90 per minute, and respirations were 20 per minute. The systolic blood pressure was 115 mm. of mercury and the diastolic pressure was 75 mm. The patient was a well-developed young male who did not appear ill. His height was 5' 8½" and his weight was 130 pounds. There was no dyspnea or cyanosis. The general physical examination was within normal limits except for the chest findings. Along the right upper sternum and right anterior chest there were scattered, dry, crackling sounds, heard best during inspiration while the patient was supine. Over the anterior mediastinum there was a characteristic Hamman's sign, with crackling and crunching synchronous with cardiac systole. No pneumothorax was detected on clinical examination. Examination of the cardiovascular system revealed no abnormalities except for a short, soft, blowing, pulmonic systolic murmur which disappeared on deep inspiration and with change of position. This was believed to be functional. The erythrocyte count was 5.2 million per cu. mm. and the hemoglobin was 16 Gm. per 100 cc. The total leukocyte count was 4,950 cells per cu. mm. with a normal differential count. The erythrocyte sedimentation rate was 0.5 mm. in the first hour (Wintrobe method). Urine examinations and a serologic test for syphilis (Kahn) were negative. Three gastric concentrates and cultures were negative for tubercle bacilli. Tuberculin skin tests using purified protein derivative, U.S.P., first and second strengths, were both negative. The chest roentgenogram (figure 2) revealed a 5 per cent right pneumothorax involving the

[1] From the College of Medical Evangelists, Los Angeles, and the Pulmonary Disease Service, Birmingham Veterans Administration Hospital, Van Nuys, California.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

apical and upper lateral portion of the right upper lobe. The lung parenchyma were normal. An electrocardiogram was normal.

The course in the hospital was entirely uneventful. The patient's temperature became normal on the day following admission and remained there throughout his stay. Mild upper chest pain on the right persisted for several days and then disappeared. The loud crackling and crunching over the anterior mediastinum were heard daily for the next five days, thereafter decreasing rapidly in intensity. A chest roentgenogram obtained one week after admission revealed no change, with the 5 per cent right pneumothorax still present. Another roentgenogram taken one week later revealed complete re-expansion of the right lung and was entirely within normal limits. The patient was discharged from the hospital (figure 3)

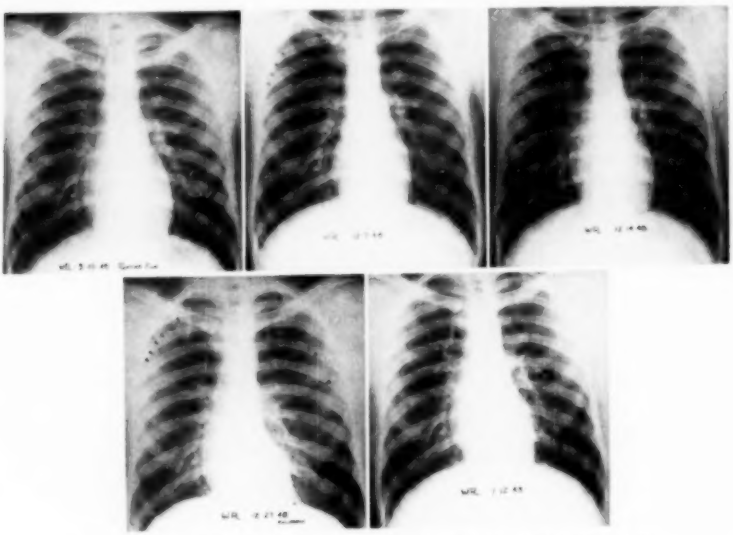


FIG. 1. (Upper left) Routine film on September 10, 1948 is negative.

FIG. 2. (Upper center) Chest film on December 7, 1948 reveals about a 5 per cent right pneumothorax.

FIG. 3. (Upper right) Chest film on December 14, 1948, prior to discharge from the hospital the first time. No pneumothorax is present.

FIG. 4. (Lower left) Chest film December 27, 1948 reveals bilateral pneumothoraces.

FIG. 5. (Lower right) Chest film on January 12, 1949 is again normal.

on December 15, 1948, with the recommendation to rest at home for one week before returning to a full normal active life.

While resting at home and prior to returning to work, he noticed a recurrence of an acute, sudden chest pain shifting from right to left and back, and bubbling noises over the sternum similar to those of his previous episodes. There was no cough, sputum, dyspnea, cyanosis, fever, or any other complaint. On readmission to the hospital December 27, 1948, he did not appear ill. His temperature was normal, the pulse rate was 80 per minute, and respirations were 20 per minute. The systolic blood pressure was 110 mm. of mercury and the diastolic pressure was 70 mm. General physical examination was again entirely within normal limits except for the chest, where decreased breath sounds were heard over the right apex. Crackling and crunching were heard again over the anterior mediastinum, both to the right and left of the sternum.

Examination of the blood revealed 5.2 million erythrocytes per cubic mm., 7,800 leukocytes per cu. mm., with a normal differential, and an erythrocyte sedimentation rate of 3 mm. in one hour (Wintrobe method). Urine examinations and a serologic test for syphilis (Kahn) were negative. The chest roentgenogram taken on admission (figure 4) revealed bilateral spontaneous pneumothoraces, with about 10 per cent collapse on the right and about 25 per cent on the left. The patient's hospital course was entirely uneventful. He was treated with nothing but bed rest. He became rapidly asymptomatic, but crunching and crackling could be heard over the anterior mediastinum daily for five days after admission. After this time crackling and crunching could be heard only occasionally and only in certain positions, and was not heard after the twelfth hospital day. The chest roentgenogram of January 6, 1949 revealed complete re-expansion of the right lung and a 5 per cent pneumothorax on the left. A chest roentgenogram one week later (figure 5) revealed both lungs to be entirely normal. The patient was discharged on January 14, 1949 and has remained well since that time.

On the first admission the final diagnoses were: (*1*) pneumothorax, benign, spontaneous, idiopathic, right lung; and (*2*) mediastinal emphysema, spontaneous. The diagnoses on his second discharge from the hospital were: (*1*) pneumothoraces, bilateral, spontaneous, idiopathic; and (*2*) emphysema, mediastinal, spontaneous.

DISCUSSION

Benign idiopathic spontaneous pneumothorax is quite common, the writers (3) having observed 100 cases. In this group, the present case is the only one to have spontaneous mediastinal emphysema recognized. Dickie (1) reported 7 patients with spontaneous pneumothorax alone, 7 with mediastinal emphysema, and 13 patients with both together. Draper (2) added another case of both occurring together. In his review of the literature, Draper found that spontaneous mediastinal emphysema and spontaneous pneumothorax occurred in young adults (94 per cent in the age group from 15 to 39 years), in males (95 per cent), and had no relationship to exertion. It is usually stated that spontaneous pneumothorax occurs in healthy young males. However, we have found that almost every one of our patients has been significantly, usually 20 to 30 pounds, underweight, although otherwise healthy. Perhaps these people have thinner pleurae than the average, and thereby more liable to tear.

Draper (2) has emphasized that, although spontaneous mediastinal emphysema and spontaneous pneumothorax often occur together, the vast majority of spontaneous pneumothoraces occur without demonstrable mediastinal emphysema. Furthermore, when the two entities occur together, the spontaneous pneumothorax is almost always on the left side, although spontaneous pneumothorax alone occurs equally on both sides. The present patient's case is of interest in that he had spontaneous emphysema and a *right* spontaneous pneumothorax on his first hospitalization, and spontaneous mediastinal emphysema and *bilateral* spontaneous pneumothoraces on his second admission.

Treatment (3) consists of simple bed rest until the lung is 85 to 90 per cent expanded, and restricted activity until full re-expansion. The rare case of tension spontaneous pneumothorax will require an indwelling intrapleural needle. After re-expansion of his lung, the patient is returned to full activity.

SUMMARY

The case of a patient who developed spontaneous mediastinal emphysema and bilateral spontaneous pneumothoraces is presented. Complete recovery occurred following a short period of bed rest.

SUMARIO Y CONCLUSIONES

Enfisema Mediastínico Espontáneo y Neumotóraces Espontáneos Bilaterales

Preséntase un caso raro de enfisema mediastínico espontáneo y neumotóraces espontáneos bilaterales. Repásanse sucintamente el enfisema espontáneo del mediastino y el neumotórax espontáneo.

REFERENCES

(1) Dickie, H. A.: Spontaneous mediastinal emphysema and spontaneous pneumothorax: A report of 20 cases, Ann. Int. Med., 1948, *28*, 618.

(2) Draper, A. J.: Spontaneous mediastinal emphysema and pneumothorax, Am. J. Med., 1948, *5*, 59.

(3) Hyde, B. and Hyde, L.: Benign idiopathic spontaneous pneumothorax, Am. J. M. Sc., 1948, *215*, 427.

PRIMARY COCCIDIOIDOMYCOSIS AND CONCOMITANT TUBERCULOSIS[1, 2]

MARCEL KAHN

(Received for publication October 31, 1949)

While investigations during the past decade have clarified somewhat our concept of coccidioidomycosis (1–5), it has also become evident that the great majority of coccidioidomycotic infections are subclinical, and can be diagnosed only by laboratory procedures. Furthermore, it has been demonstrated that the primary infection is so protean in character that differentiation from other infections is possible only by laboratory tests (5, 6). Especially difficult, and most important from a practical point of view, is the exclusion of tuberculosis (4). While in most cases the clinician will be satisfied to confirm or exclude the diagnosis of coccidioidomycosis, the occasion may arise when the very abundance of positive laboratory findings will prove confusing. The case described in this paper may serve as an example. The clinical, roentgenographic, and laboratory findings in this patient would have been convincing evidence of a primary tuberculous infection, had it not been for the rather striking evidences of a recent infection with *Coccidioides immitis*. This patient presented enough points of interest and problems of interpretation to make us believe it worth while to report his case history and laboratory findings.

CASE RECORD

D. R., a 52-year-old Filipino, was born in Vigan, Northern Luzon Island, Philippines, and has lived in the United States since 1926. Except for a short period in the Army, he was doing migratory farm work in the San Joaquin Valley, California. For three months prior to the present illness he lived in Tracy (which is located in the northern end of the Valley) while before that he had been living in the southern part of the San Joaquin Valley, near Bakersfield.

The family history was noncontributory; there was no evidence of tuberculosis or respiratory diseases. The past history did not reveal any respiratory infections of a serious nature or of unusual frequency.

The present illness was ushered in by a swelling in the left jaw which started April 15, 1948, and was accompanied by difficulty in opening his mouth. Acid foods caused discomfort. Shortly afterwards the left testicle began to swell. While the swelling of the jaw persisted for about three weeks, the testicle had returned to normal prior to admission.

On April 20, 1948 the patient went to a private physician because of a febrile respiratory infection, for which he received "one shot," presumably penicillin in oil and beeswax. He had no relief from this, and reported to the VA facility in Stockton, California, on April 28. There, a high fever was discovered and, because of evidence of pulmonary disease, he was referred to the Veterans Hospital in Livermore, California.

He was admitted there the same day, April 28, 1948, with a swinging temperature which oscillated between 99° and 104° F. during the first week of his hospital stay. His pulse rate ranged between 90 and 120 and respirations were 35 per minute, and he appeared acutely ill. He expectorated about 50 to 75 cc. of mucopurulent sputum every twenty-four hours.

[1] From the Veterans Hospital, Livermore, California.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

There was no blood and no odor from the sputum. His physical examination showed findings essentially limited to the right lung, where increased tactile fremitus was noted over the base with an increase in voice transmission, a reduction of resonance, bronchial breath sounds and moist rales. The only other pertinent finding was the swelling over the left cheek. Laboratory data on admission showed a moderately elevated total leukocyte count with granulocytosis and an increased percentage of immature granulocytes. No abnormalities were found in the urine. Specimens of sputum showed only nonpathogenic organisms on direct examination, while *H. influenzae* was the predominant organism in the forty-eight-hour culture. Neither smear nor culture showed acid-fast bacilli. The roentgenogram revealed a triangular homogeneous density in the lower central part of the right lung, with fraying towards the periphery but a rather sharply marginated superior border, which did not, however, conform to the minor fissure (figure 1). The lateral view showed that this occupied the posterior and middle basal segments and, to a lesser degree, the apical segment of the right lower lobe. In addition to this homogeneous density, a number of scalloped densities were present, visible especially in the lateral film, which presumably represented enlargement of lymphatic structures.

For the first three days after admission, the patient was started on a trial course of penicillin, 60,000 units every three hours. When the culture of the sputum showed *H. influenzae*, penicillin was discontinued and streptomycin, 0.5 Gm. twice daily, was started on May 4 1948. With neither the penicillin nor the streptomycin dosage was there any improvement in the patient's general condition or in the objective findings. Therefore, on May 10, streptomycin was increased to 0.5 Gm. four times daily, and 1 Gm. of sulfadiazine four times a day was added. Throughout the month of May, the patient's temperature remained elevated, but about May 15 the oscillations became less steep and, although the temperature remained swinging in character, the peaks became gradually lower. On May 21, sulfadiazine was discontinued and streptomycin decreased to 0.5 Gm. twice a day. Throughout this period repeated sputum culture, smear, and concentrate examinations were performed. Of about 20 such tests, two cultures on May 7 and May 19, and one seventy-two-hour concentrate on May 17 were reported positive for acid-fast bacilli. A tuberculin skin test with PPD, second strength, on May 14 was negative. A coccidioidin skin sensitivity test was negative 1:1,000 and 1:100 on May 12. On May 18, the patient's serum showed a complement fixation up to 1 to 4 and a precipitin reaction positive at 1 to 40. The tests were repeated on May 28 and at that time showed a rise of complement fixation up to 1 to 32, while the precipitins remained at 1 to 40. In the beginning of June the patient appeared to be clinically cured. He did not have any fever and felt well. His sputum (of which ten cultures, concentrates, and direct smears were taken) remained negative for acid-fast bacilli, but on June 3 the tuberculin skin test showed a positive reaction on PPD second strength. The coccidioidin skin test was also repeated in view of the suggestive serologic findings and showed a positive reaction with 1:100 dilution. Complement fixation tests on June 10 showed positive reaction at 1 to 64, precipitins positive at 1 to 40. A sputum culture was obtained on June 14 and yielded a growth of *Coccidioides immitis*, which was verified by injection into a guinea pig. Because of marked improvement, streptomycin was discontinued on June 15. On June 22 the complement fixation test was repeated and showed the same high titer of 1 to 64, but the precipitins had vanished to a point where they were positive only in the undiluted serum.

Between July and October, the patient was clinically well, and chest roentgenograms showed a very slow progressive clearing of the lesion (figure 2). Repeated smears, concentrates, and cultures of the sputum during this period were negative for acid-fast bacilli. The complement fixation test remained at a titer of 1 to 64 for coccidioidin, while the coccidioiditis precipitins had disappeared. A bronchoscopy was done on October 1 and showed some edema and injection of the entire right bronchial tree, with narrowing in the region of the right middle lobe bronchus. The lipiodol mapping of the bronchial tree showed normal filling except of the apical segment of the right lower lobe, which remained unfilled. At about the same time the patient developed a small amount of fluid in the right costophrenic angle, which cleared up spontaneously within one month. In November

FIG. 1. Roentgenogram of chest on May 6, 1948.

FIG. 2. Roentgenogram of chest on August 11, 1948.

These roentgenograms demonstrate the slow and incomplete clearing of the lesion in the right lung.

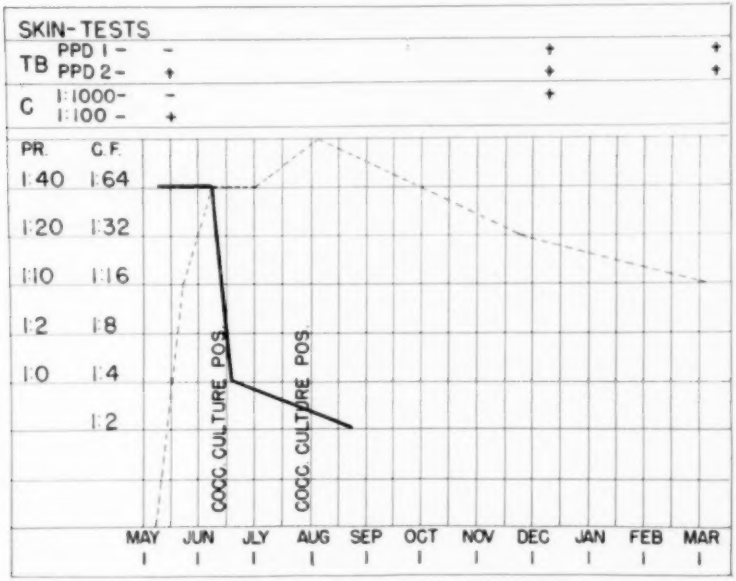


FIG. 3. Graph: The slow increase and decline of the complement fixation titer (C.F.—broken line) compared to the beginning high precipitin titer and rapid fall (PR.—solid line). The conversion of the tuberculin (PPD, Nos. 1 and 2) and coccidioidin (1:1,000 and 1:100) skin tests is shown above the graphs.

the complement fixation dropped to 1 to 32, the PPD test, first strength, was positive to 3 plus, the coccidioidin skin test 1:100 was positive to 3 plus (figure 3). Clinically the pa-

tient appeared well and was ambulatory. In January 1949 the patient had another isolated positive sputum culture for acid-fast bacilli. Numerous cultures, concentrates, and direct smears for three months before and after this positive culture did not show acid-fast bacilli. The coccidioidin complement fixation test was positive at 1 to 16; precipitins were negative. The patient was fully ambulatory and had no complaints.

COMMENT

The laboratory findings in this patient constitute convincing evidence of a recent coccidioidomycotic infection (5, 7, 8, 9). A few factors, however, deserve scrutiny. The clinical course fits rather well into the pattern of coccidioidomycosis as described by numerous observers, although the signs in the chest are somewhat more pronounced than is usually the case. But the time of infection is not common. It has been pointed out that the dry season is a more likely time for contracting the disease than spring, even though the winter 1947 to 1948 was below average in rainfall (10). Furthermore, if it be assumed that the incubation period is usually between three and seven weeks, the place of infection would have been somewhere near Tracy in the northern San Joaquin Valley, a site somewhat outside of the endemic area (11), although close enough to it.

There should be no logical reason why a person with coccidioidomycosis should not contract tuberculosis at the same time or subsequent to the mycotic infection (12). Both diseases in the same patient have been described repeatedly (6, 13), but, as far as could be determined from the literature, a simultaneous infection with both organisms has not been described. Whether this is such a case is debatable. In the first place, it is unusual to find a 52-year-old migratory Filipino farm-worker who has not been previously infected with tuberculosis. Anergy to tuberculin has been found not only in massive tuberculous infection and several specific diseases, but also in nonspecific fulminating diseases (14). To our knowledge, parotitis has never been described as one of the diseases to produce this anergy, and neither has coccidioidomycosis. The patient was not ill enough to be classed "critically ill with a fulminating disease." In view of the gradual conversion of a negative tuberculin test to a positive one, it is reasonable to assume that a primary tuberculosis infection occurred. If the tuberculosis is considered to be a primary infection, it still is not proved that the two infections were acquired simultaneously. There remains the possibility that the patient with a primary coccidioidomycosis was admitted to this hospital, which cares mainly for tuberculous patients, and was exposed here to tuberculosis. The time for conversion of a negative tuberculin test has been set between three and eight weeks (15), the same time as that required for the appearance of a positive coccidioidin test. The almost simultaneous appearance of both skin reactions would prove a simultaneous infection only if one assumes that the incubation period and the sensitization period of both are equal in the same individual, a fact which has never been established.

Whether the growth of *H. influenzae* in the sputum culture is a significant part of the picture cannot be determined. The influenza bacillus is a common respiratory saprophyte, but influenza bacillus pneumonia in adults is exceedingly rare. Moreover, the course of the patient's illness after admission to the hospital was decidedly more suggestive of a mycotic infection.

SUMMARY

A case of primary coccidioidomycosis and coexistent primary tuberculosis is presented. The difficulties in evaluating the respective parts played by the two diseases in producing the clinical symptoms and roentgenographic abnormalities are discussed.

Acknowledgment

The serologic work referred to in this paper was done by Dr. C. E. Smith's laboratory at Stanford Medical School and interpreted by him. The author gratefully acknowledges his assistance and helpful suggestions.

REFERENCES

(1) Dickson, E. C.: Valley fever, California & West. Med., 1937, *47*, 151.
(2) Farness, O. J.: Coccidioidomycosis, J. A. M. A., 1941, *116*, 1749.
(3) McCracken, J. P.: Coccidioidomycosis, North Carolina M. J., 1945, *6*, 25.
(4) Yegian, D., and Kegel, R.: *Coccidioides immitis* infection of the lung, Am. Rev. Tuberc., 1940, *61*, 393.
(5) (a) Smith, C. E.: Parallelism of coccidioidal and tuberculous infections, Radiology, 1942, *38*, 643.
(b) Smith, C. E.: Coccidioidomycosis, M. Clin. North America, 1943, *27*, 790.
(c) Smith, C. E.: Recent progress in pulmonary mycotic infections, California Med., 1947, *76*, 3.
(d) Smith, C. E., Beard, R. R., Saito, M. T.: Pathogenesis of coccidioidomycosis, Ann. Int. Med., 1948, *29*, 623.
(6) Cherry, C. B., and Bartlett, A. G.: The diagnosis of acute *Coccidioides immitis* infections, M. Bull. U.S. Army, 1946, *5*, 190.
(7) Carter, R. A.: The roentgen diagnosis of fungus infections of the lung, Radiology, 1942, *38*, 649.
(8) Colburn, J. R.: Roentgenological types of pulmonary lesions in primary coccidioidomycosis, Am. J. Roentgenol., 1944, *51*, 1.
(9) Winn, W. A., and Johnson, G. H.: Primary coccidioidomycosis, Ann. Int. Med., 1942, *17*, 407.
(10) Smith, C. E., Beard, R. R., Rosenberger, H. G., and Whiting, E. G.: Effect of season and dust control on coccidioidomycosis, J. A. M. A., 1946, *132*, 833.
(11) Aronson, J. D., Saylor, R. M., and Parr, E. I.: Relationship of coccidioidomycosis to calcified pulmonary nodules, Arch. Path., 1942, *35*, 31.
(12) Greer, A. E., and Gemoets, H. N.: Coexistence of pathogenic fungi in certain chronic pulmonary diseases, Dis. of Chest, 1943, *9*, 212.
(13) Study, R. S., and Morgenstern, P.: Coexisting pulmonary coccidioidomycosis and tuberculosis, New England J. Med., 1948, *238*, 837.
(14) Furcolow, M. L.: Depression of skin sensitivity by critical illness, Pub. Health Rep., 1948, *63*, 1290.
(15) Wallgren, A.: Erythema nodosum and pulmonary tuberculosis, Lancet, 1938, *1*, 359.

Editorial

Implications of Rapidly Effective Tuberculosis Therapy

If a new drug or combination of drugs, safe and highly effective in the treatment of tuberculosis, should be discovered in the year 1950, one might be tempted to assume that eradication would take place quickly and automatically. In reality, the responsibilities of those charged with tuberculosis-control activities would be immediately increased.

There would be a moral obligation, enforced by a vocal public opinion, to see that every case, in any stage of the disease, received the new therapy. This could be very expensive, even in terms of known cases under medical supervision. The immediate demand for hospital beds might be so tremendous as to constitute an emergency. As a secondary result, patients with permanent lung damage who could be benefited by surgery would tend to crowd the hospitals unless there were an increase in surgical services.

If the full value of such a discovery were to be realized, all case-finding procedures would have to be greatly intensified. With complete eradication made more of a possibility within a relatively short time, every effort would have to be made to find all cases. It is conceivable that the discovery and treatment of primary cases of tuberculosis would be practical, and even mandatory, under such circumstances so that endogenous relapses of the future would be prevented.

The shortage of hospital beds and physicians trained in tuberculosis work would probably lead to a trial of home treatment by nurses or other auxiliary workers under medical guidance. Certainly ambulant treatment through established clinics would have to be used if at all practical. The rapid discovery, treatment and discharge of patients would also greatly increase the need for public health nursing, rehabilitation, social work, and health education services. The shortage of personnel would become increasingly acute.

Is this all a dream? Perhaps so, but streptomycin and PAS have already produced some amazing results. Newer and possibly more promising drugs are now receiving preliminary tests. We have numerous examples of other bacterial diseases, both acute and chronic, for which rapid cures are now available. There are good grounds for optimism, but we should not forget that, if our hopes for rapid effective treatment are fulfilled, our task will be magnified rather than reduced, and we shall need every resource we can mobilize for some time to come.

FLOYD M. FELDMANN

Letters to the Editors

SERUM GAMMA-GLOBULINS IN PULMONARY TUBERCULOSIS[1]

To the Editors of the American Review of Tuberculosis:

The recent publication by Kunkel and his co-workers (Gastroenterology, 1948, *11*, 499) of a rapid and simple method for the determination of gamma-globulin content of human serum has led us to undertake an investigation of the gamma-globulin content of the serum in the course of pulmonary tuberculosis. The reason for making such a study was the previous demonstration by Seibert and her co-workers (J. Clin. Investigation, 1947, *26*, 90) by the electrophoretic method that there was "a slight but significant rise in the mean gamma-globulin component in early tuberculosis" and her suggestion that it would be "of interest to determine whether the rise in this component has any prognostic value in differentiating potentially dangerous cases from the self-healing type . . . since antibodies in tuberculosis have also been found in this fraction." While the facilities for making a large number of serial electrophoretic determinations on a large number of tuberculous patients are not customarily available to the average clinical laboratory, the Kunkel method, which can be rapidly carried out in the ordinary clinical laboratory, would seem to be admirably suited for such a study.

To date we have studied 150 tuberculosis patients by this method, and in many have performed simultaneous determinations of the serum albumin and globulin. In addition, determinations of cephalin flocculation, thymol turbidity, bromsulfalein excretion, serum bilirubin, cholesterol, and esters were also made. In all patients, erythrocyte sedimentation rates (ESR) were measured. Because of the chronicity of the disease, such a study, in order to have significance, will have to be a long-term investigation. The results over a six-month period appear to be of sufficient interest, however, to warrant summarizing the main findings at this time for other workers who might be interested in utilizing these relatively simple methods and thus evaluating them on a large scale.

Thus far we have not been able to confirm Seibert's findings of a progressive increase in gamma-globulin content which parallels the extent of the disease; there appears to be a good deal of overlapping of values in the minimal, moderately and far advanced active cases. However, all of the 20 patients whose lesions were fully arrested for variable periods of time had values of less than 8 turbidity units by the Kunkel method. In 28 of the patients, values above 10 turbidity units, some as high as 37, were determined. While these were for the most part moderately advanced and far advanced cases of active tuberculosis, in many instances the exact trend still remains to be determined by further observation. All of these patients had total globulin values of 2 Gm., or more, per 100 cc. Of the 28 cases with turbidity values above 10, significant elevations of ESR by the Westergren method were present in only 11. In several patients we have noted a drop in gamma-globulin content following successful pulmonary resection or spontaneous cavity closure. We are checking the accuracy of the Kunkel method by simultaneous electrophoretic determinations in a suitable number of cases.

In 17 patients, positive cephalin flocculation reactions were present without other labo-

[1]Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

ratory or clinical evidence of hepatic disease. We believe that these positive reactions are due to changes in the serum protein fractions but not the gamma component, since there was no parallel between positive cephalin flocculation and elevated gamma-globulin. The thymol turbidity reaction in all but 2 of these patients was within normal limits, and in those the elevation was slight. In all but 3 of these patients, the tuberculosis was considered to be actively progressive at the time of this report. Only 6 of these 17 patients had significantly elevated ESR.

Of additional interest is the recent report of Mertens and Bunge (Am. Rev. Tuberc., 1949, *61*, 20) that "electrophoresis of the plasmas of tuberculous patients permitted recognition of the fact that in exudative processes an increase at the alpha-globulin predominates, while in chronic, proliferating, cirrhotic forms, the . . . . fibrinogen and the gamma-globulin increase markedly . . . . Heilmeyer pointed out that under thiosemicarbazone treatment a typical diminution of the alpha-globulin and an increase of the gamma-globulin is obtained." These findings, in patients not treated with thiosemicarbazone, appear to be at variance with those reported by Seibert as well as with our own. In view of the elevated gamma-globulin in hepatic disease reported by Kunkel, one naturally wonders if this response to thiosemicarbazone reported by these workers may not rather be interpreted as further evidence of the hepatotoxicity of this drug.

The observation of Seibert that in pulmonary tuberculosis there is an increase in gamma-globulin and a decrease in albumin; in pulmonary carcinoma, a decrease in gamma-globulin; and in pulmonary sarcoidosis, an increase in gamma-globulin as well as albumin; would indicate a possible use of the Kunkel method in the differential diagnosis of these three conditions.

We suggest the routine use of the easily performed Kunkel determination of gamma-globulin and the cephalin flocculation reaction (or perhaps the improvement recently suggested by Steinberg (J. Lab. Clin. Med., 1949, *34*, 1049) of a stable cholesterol-desoxycholic acid reagent) in pulmonary tuberculosis as possible prognostic laboratory indices of greater value than the ESR.

MAURICE J. SMALL

TUBERCULOSIS SERVICE
HALLORAN VETERANS ADMINISTRATION HOSPITAL
STATEN ISLAND, NEW YORK
February 26, 1950

BOOKS

GREGORY KAYNE, WALTER PAGEL, AND LAURENCE O'SHAUGHNESSY: *Pulmonary Tuberculosis. Pathology, Diagnosis, Management and Prevention. Revised and partly rewritten by Walter Pagel, F. A. H. Simmonds, N. MacDonald, and T. Fatti. Second Edition. Pp. 720, with illustrations, Oxford University Press, New York, 1948, Price $18.50.*

The first edition of this work which was published in 1939 won immediate recognition on both sides of the Atlantic as the best contemporary textbook on pulmonary tuberculosis. During the nine-year interval between the original edition and this first revision the book retained its position of leadership, being supplemented rather than challenged by the shorter and more personal volume by Max Pinner.

Of the three original authors, only Walter Pagel survived to complete the work of revision. Laurence O'Shaughnessy died on active service in 1940 and Gregory Kayne passed on after a long illness in 1945, but not without contributing early drafts of chapters for the new edition. The clinical sections, originally allotted to Kayne alone, were finally rewritten by Doctor MacDonald and Doctor Simmonds. The surgical sections were rewritten by Mr. Fatti.

Much new material has been added and in most respects the book has been brought thoroughly up to date. It is unfortunate, however, that the work of revision was taking place at the time when the development of antimicrobial therapy was in its early beginning and the place of streptomycin was yet insecure and ill defined. This important subject had, therefore, to be relegated to an appendix. Even at the time of publication (1948), but more clearly in the last two years, it has become impossible to discuss any aspect of the management of tuberculosis without considering *pari passu* the problem of adjuvant antimicrobial therapy. This cannot be regarded as a criticism, since at the present time there is no textbook to which the student or practitioner can turn for guidance in these matters. Because the subject of antimicrobial therapy is still in a state of flux, especially with respect to the precise indications for streptomycin and other agents, and to the optimum dosage regimens, it is doubtful whether this aspect of tuberculosis therapy could as yet be satisfactorily interwoven into a text so as not to require almost immediate revision upon publication.

The extensive revision by Pagel of Part I on pathology presents much new material, including a rewriting of the chapter on resistance, and new passages in the section on primary tuberculosis concerning congenital tuberculosis, double pulmonary and intestinal infection, and primary infection in adults. In the same chapter (on the evolution of tuberculosis in man) the pathogenesis of bronchogenic tuberculosis (phthisis) has been accorded a new representation based on the author's recent studies of post-mortem material in which the significance of late primary infection became apparent. This is the most succinct presentation of the fundamental problem of the origin of phthisis known to the present reviewer and it resolves much of the former controversy between the proponents of "exogenous" versus those of "endogenous" reinfection. Pagel, who prefers the term "superinfection" in this connection, criticizes the epidemiologic arguments advanced in favor of exogenous superinfection and presents morbid-anatomical evidence in favor of the frequency of the development of phthisis by endogenous superinfection from late primary infections occurring in adults.

In Part II, on diagnosis, emphasis is well placed, in accordance with the importance of the subject, on the evaluation of asymptomatic disease discovered by roentgenographic

surveys. American authorities would perhaps devote more space to differential diagnosis, with special regard to asymptomatic cancer of the lung. The chapter on physical diagnosis is concise, with the emphasis properly placed on the limitations of this method of diagnosis. In the chapter on bacteriologic examinations there is an evaluation of the laryngeal swab technique which should recommend this to wider use in this country as an alternative method to gastric lavage, especially for outpatients. The chapter on pleurisy with effusion reviews this frequently neglected subject in great detail and re-emphasizes the importance of treating so-called idiopathic pleurisy with effusion as active tuberculosis in the absence of clear evidence of another cause.

A new section on the management of pregnancy and child-bearing in tuberculosis has been added which is notable for its common-sense approach to these problems, especially with respect to the consideration which must be given to social and economic factors in advising whether a pregnancy should be interrupted or permitted to continue.

The final part of the book on epidemiology and prevention, revised by Doctor Simmonds, contains interesting new material on tuberculin surveys and on the morbidity and mortality rates in England and other European countries during and after World War II. The subject of BCG vaccination is presented on the basis mainly of Scandinavian (and some American) studies, experience with the matter being small in Britain.

In an appendix both the British (Ministry of Health) and the American (National Tuberculosis Association) classifications of pulmonary tuberculosis are given, which is a useful feature in connection with the use of the book for teaching in this country.

The over-all excellence of the first edition has been retained in this difficult and necessarily extensive revision after so many years. The interval of nine years between the editions, as is explained in the preface, was due in large part to the long illness and death of Doctor Kayne. Probably the war was also a factor in the unusually long interval. It is to be hoped that the present group of authors will find it possible to bring out new editions at more frequent intervals. The basic work is too good to allow the book to fall much behind fresh progress; and there will for many years be need for a book of this range and character.

CARL MUSCHENHEIM

MARGUERITE F. HALL: *Public Health Statistics. Second Edition. Pp. 441, Paul B. Hoeber, Inc., New York, 1949, Price $7.50.*

This is an attractive book without the formidable appearance of some textbooks on statistics. The reader will find the type and non-glare paper easy on the eyes. In the preface to the first edition, the author states that "This book is intended for use as a text for a basic course in public health statistics and as reference material in health departments." She also intimates that the presentation might be considered oversimplified by some people. That certainly is not true if the book is to be used by physicians or other professional people who have had no previous introduction to the subject.

The earlier chapters in the book dealing with the common definitions, need for, and use of, vital statistics, and the presentation of data are well illustrated and explained in a manner suited to the uses of a beginning student. The later chapters will be heavier going for the "adults who have little or no training in the intricacies of mathematics."

The statistical processes are well described, but one has the impression of speeding by helpful guideposts without time to consider them carefully. Undoubtedly, these little gaps would be covered by any teacher presenting a course.

The flow of material from the simple to the more complex might have been improved

by some rearrangement. The very last chapter entitled "Prerequisites to the Application of Statistical Methods" discusses such basic matters as selection of material, allocation to groups, uniformity of data, and defining the problem. This could have fitted in well with Chapter II, "General Principles of Computation and Handling of Mass Data," or Chapter XVI, "Mass Data: Preliminary Definitions."

Probably physicians doing clinical research will find Chapter XXI, "Measures of Reliability" of most use. Certainly the sampling concept with its applications and limitations is coming to be more appreciated. This chapter might well be read before Chapter XVIII on "Measures of Variability."

The life table seems to have a very brief treatment when introduced in Chapter VII, but the description in Chapter XIV is good. Why it first appears in Chapter VII is not made clear.

In spite of this impression that the chapters of the book could have been reshuffled with an improvement in its usefulness to those being introduced to public health statistics, the book will be of value to more experienced workers as a quick reference for the commoner procedures.

FLOYD M. FELDMANN

SELMAN A. WAKSMAN (Editor): *Streptomycin, Its Nature and Practical Applications. Pp. 618 with illustrations, The Williams and Wilkins Co., Baltimore, Md., 1949, Price, $10.*

This book assembles a vast amount of information on streptomycin in a single volume and in a form which should prove to have a wide field of usefulness. The scope of the book includes an account of the development of streptomycin, methods of production and isolation, chemistry, and various aspects of the antibacterial activity of the drug *in vitro*, as well as a fairly comprehensive discussion of the clinical uses of the drug. The book presents in well-organized fashion a series of forty-six separate papers on streptomycin, and the editor is to be congratulated on his choice of authors. The list of contributors represents an impressive number of those investigators who have played important parts in the development of streptomycin both in the laboratory and in clinical practice. In general, the material contained in the individual chapters appears to be accurate and authoritative. As might be expected, a considerable amount of repetition of information occurs throughout the book. Because of the subject and the fact that so much of the information is new, the authors too frequently have felt constrained to describe in detail, or to document, certain points to an extent which detracts from its readability. It seems also that much unnecessary repetition of references could have been avoided by having only a single bibliography, instead of one at the conclusion of each chapter.

Outstanding among the sections in this book is Section II which covers the antibacterial and pharmacologic properties of streptomycin. The introductory chapter by Youmans and Fisher on the *in vitro* action of streptomycin is particularly valuable. Among other things in this chapter is a discussion of various factors which influence the *in vitro* activity of streptomycin, and a standard procedure is recommended for routine use in testing bacterial sensitivity to streptomycin. It has been overlooked too frequently that variations in the culture medium and other factors which go to make up the usual sensitivity test may profoundly affect the results of these tests. Unfortunately, the decision whether a patient will receive streptomycin is based very often on the results of these determinations, and one may hope that this standard procedure will be generally adopted. Section II also contains one of the poorest chapters, a discussion of synergism between antibacterial substances with special reference to streptomycin. The subject seems to have little place in a book of this type, and the discussion seems unnecessarily prolonged.

The subjects covered in Section III, clinical uses of streptomycin, are well chosen and reasonably complete. Three chapters in this section as well as two in Section II are devoted solely to tuberculosis. The authors summarize well our present state of knowledge concerning the *in vitro* action of streptomycin on tubercle bacilli, as well as the use of this drug in the treatment of human tuberculosis.

Doctor Waksman's book should be widely read and should serve as a ready source of authoritative information on streptomycin not only for the clinician but for those in the pharmaceutical industry, as well as microbiologists and veterinary physicians.

RALPH TOMPSETT

INDEX OF SUBJECTS AND AUTHORS

ABRAMSON, SAMUEL. *See* LURIE, MAX B., *et al.*

Abscess, Acute lung, 474

Acid, kojic, as inhibitor of tubercle bacilli, 739

——, para-aminosalicylic, Febrile reactions to, 643

——, ——, for tuberculosis, 226

——, ——, in pulmonary tuberculosis, 597

——, ——, —— —— and extrapulmonary tuberculosis, 613

——, ——, —— intestinal tuberculosis, 621

ACKERMAN, ALFRED J., AND MOYER, JOHN J. Sarcoidosis: A clinical and roentgenological study of twenty-eight cases, 299

ADCOCK, JOHN. *See* OWEN, CORA RUST, *et al.*

Adenomatosis, alveolar, 131

——, pulmonary, 131

Airborne infection. *See* Infection.

Air evacuation of tuberculous military patients, 678

—— travel in tuberculosis, 678

ALEXANDER, JOHN. Postoperative management of thoracoplasty patients, 57

AMBERSON, J. BURNS. *See* LATTIMER, JOHN K., *et al.*

AMERICAN TRUDEAU SOCIETY:

Report of Clinical Subcommittee: Current status of drug therapy in tuberculosis, 436

Report of the Laboratory Subcommittee of the Committee on Medical Research and Therapy, and of the Subcommittee on Evaluation of Laboratory Procedures of the Committee on Revision of Diagnostic Standards, 274

Report of Subcommittee on Clinical Classification of Committee on Revision of Diagnostic Standards: Classification of pulmonary tuberculosis, 760

Report to Clinical Subcommittee on German experience with thiosemicarbazone, 145

Amines, simple primary, *in vitro* and *in vivo*, 407

ANGELL, FRANKLIN L., AND KENDIG, EDWIN L., JR. Streptomycin and Promizole in the treatment of widespread pulmonary tuberculosis in a 19-day-old infant (case report), 747

Antibody response and penicillin, 24

Antihistamine, Effect on tuberculin reaction (letters to the editors), 442

Antihistaminic drugs, Effect of, upon tuberculin reaction, 735

Antituberculous activity of thiosemicarbazones, 1, 8

—— —— —— *in vitro* and *in vivo*, 8

Appendicitis during pneumoperitoneum treatment, 353

ARANY, L. S., AND LEWIS, W. G. Tuberculous infection with streptomycin-resistant organisms (case report), 881

Asphyxia, fatal, from Lucite plombage, 422

AUERBACH, OSCAR. Pleural, peritoneal, and pericardial tuberculosis. A review of 209 cases uncomplicated by treatment or secondary infection, 845

Aureomycin in treatment of tuberculosis, 875

BARRIST, ELLIS M., AND GRAUB, MILTON. The effect of antihistaminic drugs upon the tuberculin reaction, 735

BASS, H. E. Pulmonary coccidioidomycosis cases (letter to the editors), 158

Bacilli, tubercle, Direct method for determination of sensitivity of, to streptomycin, 569

——, ——, Dissemination of, in experimental tuberculosis in the guinea pig, 399

——, ——, isolated from patients treated with streptomycin, 705

——, ——, Kojic acid as inhibitor of, 739

——, ——, Methods for isolating, 563

——, ——, Resistance of, to chemotherapeutic agents, 483

——, ——, Streptomycin-resistant, 719

Bacillus, tubercle, Effects of products of sarcoid lymph nodes on, 730

——, ——, Extraction of proteins and other constituents from, 798

Bed rest, "modified," in minimal tuberculosis, 809

BEHNISCH, ROBERT, MIETZSCH, FRITZ, AND SCHMIDT, HANS. Chemical studies on thiosemicarbazones with particular reference to antituberculous activity, 1

Benemid, Influence of, on para-aminosalicylic acid plasma concentrations, 862

Berke, Rudolph. Contagiousness of coccidioidomycosis (letters to the editors), 441

Birkeland, Jorgen M., and Sandage, Curtis. Effect of intravenous tuberculin injections on subsequent tuberculin skin reactions in hypersensitive rabbits, 556

Black, Thomas C., and Evans, Elwyn. The electrocardiogram in pneumoperitoneum: Including augmented unipolar limb leads and unipolar chest and esophageal leads, 335

Black, Thomas C. *See* Jones, Russell S., *et al.*

Bloch, Hubert. Enzymatic characteristics of suspensions of different mycobacteria (letters to the editors), 270

Bloomer, William E., and Major, James W. The effect of penicillin on wound infection and other complications after thoracoplasty, 346

Boeck's sarcoid, 730

Bogen, Emil, Loomis, Russell N., and Will, Drake W. Para-aminosalicylic acid treatment of tuberculosis, 226

Boger, William P., and Pitts, Forrest W. Influence of *p*-(Di-n-Propylsulfamyl)-benzoic acid, "Benemid," on para-aminosalicylic acid (PAS) plasma concentrations, 862

Boltjes, Ben. *See* Lee, Henry F., *et al.*

BOOKS:

Bertwistle, A. P. A Descriptive Atlas of Radiographs, an Aid to Modern Clinical Methods, 758

Cummings, S. Lyle. Tuberculosis in History, 592

Di Rienzo, S. Radiologic Exploration of the Bronchus, 757

Hall, Marguerite F. Public Health Statistics, 896

Johnstone, Rutherford T. Occupational Medicine and Industrial Hygiene, 593

Kayne, Gregory, Pagel, Walter, and O'Shaughnessy, Laurence. Pulmonary Tuberculosis. Pathology, Diagnosis, Management and Prevention, 895

Massey, Arthur. Modern Trends in Public Health, 273

Merrill, Vinta. Atlas of Roentgenographic Positions, 757

Waksman, Selman A. (Editor). Streptomycin, Its Nature and Practical Applications, 897

Wittkower, Eric. A Psychiatrist Looks at Tuberculosis, 272

Zacks, David. Photoradiography in Search of Tuberculosis, 594

Bornstein, Siegbert, and Schaff, Burnett. Appendicitis during pneumoperitoneum treatment, 353

Braham, Stanley. *See* Lattimer, John K., *et al.*

Bronchiectasis and tuberculosis, Relationship between, 387

Bronchitis, tuberculous, in pulmonary resection, 185

Bronchogenic carcinoma. *See* Carcinoma.

Bronchoscopies, Review of, 355

Buckles, Maurice G., and Neptune, Wilford, B. Tuberculous bronchitis in pulmonary resection, 185

Bulla, emphysematous, complicated by hemorrhage and infection, 742

——, ——, Surgical drainage of, 742

Bunge, Rolf, and Mertens, Anton. The present status of the chemotherapy of tuberculosis with Conteben, a substance of the thiosemicarbazone series, 20

Bunn, Paul A. Specific therapy for tuberculous meningitis (editorial), 263

Cancer, lung, Cytological diagnosis of, 60

Carcinoma, bronchogenic, and pulmonary tuberculosis, 369

——, ——, Tuberculoma of the lung simulating, 431

Carstensen, Bo. Para-aminosalicylic acid (PAS) in pulmonary and extrapulmonary tuberculosis, 613

Cerebral vessels, Thrombosis of, with necrosis of the basal nuclei, 247

Chemical studies on thiosemicarbazones, 1

Chemotherapeutic agents, Resistance of tubercle bacilli to, 483

Chemotherapy of tuberculosis, 407

—— —— —— with Conteben, 20

Children, miliary and meningeal tuberculosis in, Streptomycin-promizole therapy for, 159

Clagett, Theron O. *See* Hedberg, Gustaf, A., *et al.*

Clerf, Louis H., and Herbut, Peter A. The value of cytological diagnosis of pulmonary malignancy, 60

Coccidioidomycosis and concomitant tuberculosis, 887
——, Contagiousness of, 95, 106
——, —— ——, (letters to the editors), 441
——, pulmonary (letters to the editors), 158
COHEN, DAVID H. A comparison between an aneroid spirometer and a water spirometer, 582
COLLINS, MARTHA D., AND FISHER, HYMAN. A case of generalized hemangio-sarcomatosis erroneously considered as generalized tuberculosis, 257
CONANT, NORMAN F. Laboratory diagnosis of pulmonary mycoses, 690
Contagiousness of coccidioidomycosis, Studies of, 95, 106
Conteben, Chemotherapy of tuberculosis with, 20
Control study PAS, 597
COPE, J. H. *See* YERUSHALMY, J., *et al.*
CUTHBERT, JAMES. Tuberculous empyema: Clinical course and management. With review of 146 cases, 662
Cytological diagnosis of pulmonary malignancy, 60

DANIELS, MARC. Scientific appraisement of new drug in tuberculosis (editorial), 751
DAVEY, WINTHROP N. *See* OWEN, CORA RUST, *et al.*
DAVIN, JULIA R., AND ROGERS, ARTHUR E. T. Febrile reactions to para-aminosalicylic acid, 643
Dissemination of tubercle bacilli in experimental tuberculosis in the guinea pig, 399
Dogs, Experimental tuberculosis in, 77
DOMAGK, GERHARD. Investigations on the antituberculous activity of the thiosemicarbazones *in vitro* and *in vivo*, 8
DOUB, LEONARD, AND YOUMANS, GUY P. Studies in tuberculosis chemotherapy. I. Simple primary aromatic amines, *in vitro* and *in vivo*, 407
Drainage, surgical, of emphysematous bulla, 742
DROLET, GODIAS J., AND EDWARDS, HERBERT R. The implications of changing morbidity and mortality rates from tuberculosis, 39
Drugs, new, in tuberculosis, Scientific appraisement of (editorial), 751
DYE, WILLIAM E. Streptomycin-resistant tubercle bacilli, 719

EDITORIALS:
Implications of rapidly effective tuberculosis therapy, 892
Scientific appraisement of new drugs in tuberculosis, 751
Specific therapy for tuberculous meningitis, 263
Tuberculosis on the Navaho reservation, 586
EDWARDS, HERBERT R., AND DROLET, GODIAS J. The implications of changing morbidity and mortality rates from tuberculosis, 39
EISENMAN, WILLIAM. *See* LEE, HENRY F., *et al.*
Electrocardiogram in pneumoperitoneum, 335
ELMORE, FRANCIS H., AND ROSENTHAL, SOL ROY. Studies on the contagiousness of coccidioidomycosis:
II. The fate of spherules in sputum exposed out of doors, 95
III. Infection in guinea pigs by contact with diseased animals, 106
Emphysema, spontaneous, mediastinal, and bilateral spontaneous pneumothoraces, 883
Emphysematous bulla complicated by hemorrhage and infection, 742
—— ——, Surgical drainage of, 742
Empyema, tuberculous: Clinical course and management, 662
Enzymatic characteristics of suspensions of different mycobacteria (letters to the editors), 270
ERLICH, HENRY. *See* ROBERTS, E. GWYN, *et al.*
EVANS, ELWYN, AND BLACK, THOMAS C. The electrocardiogram in pneumoperitoneum: Including augmented unipolar limb leads and unipolar chest and esophageal leads, 335
Exacerbations, post-thoracoplasty, 648
Extrapulmonary tuberculosis. *See* Tuberculosis.

FELDMANN, FLOYD M. Implications of rapidly effective tuberculosis therapy (editorial), 892
FISHER, HYMAN, AND COLLINS, MARTHA D. A case of generalized hemangio-sarcomatosis erroneously considered as generalized tuberculosis, 257

Friedländer's pneumonia, 465
FRIEDMAN, ELI, AND SILVERMAN, IRVING. The effect of antihistamine medication on the tuberculin reaction (letters to the editors), 442

Gamma-globulins, serum, in pulmonary tuberculosis (letters to the editors), 893
Gastric tuberculosis. *See* Tuberculosis.
GEEVER, ERVING F., AND STONE, WILLIAM F., JR. Fatal asphyxia as a complication of Lucite plombage (case report), 422
Gelatin foam, Use of, in thoracoplasties, 193
Genitourinary tuberculosis. *See* tuberculosis
GOMORI, GEORGE. The distribution of iron in tuberculous granulation tissue, 560
GORDON, BURGESS. *See* MOTLEY, HURLEY L., *et al.*
GRAUB, MILTON, AND BARRIST, ELLIS M. The effect of antihistaminic drugs upon the tuberculin reaction, 735
GREENBERGER, MONROE E., AND SPORER, ANDREW. Experimental studies on the pathogenesis and prognosis of renal tuberculosis, 508
Guinea pig, Dissemination of tubercle bacilli in experimental tuberculosis in, 399
GUNN, F. D., AND SHEEHY, JOHN J. Experimental tuberculosis in the dog. Comparison of lesions in puppies and in mature dogs, 77

HABEEB, WILLIAM J., AND REISER, HOWARD G. Pneumoperitoneum with phrenic paralysis for pulmonary tuberculosis, 323
HARKNESS, J. T. *See* YERUSHALMY, J., *et al.*
HECKLY, ROBERT J., AND WATSON, DENNIS W. Extraction of proteins and other constituents from the tubercle bacillus, with some observations on their chemical and biological properties, 798
HEDBERG, GUSTAF, A., SEYBOLD, WILLIAM D., AND CLAGETT, THERON O. The use of gelatin foam (Gelfoam) in thoracoplasties, 193
HELLER, PAUL. *See* STEINBACH, M. MAXIM, *et al.*
Hemangio-sarcomatosis, generalized, erroneously considered as generalized tuberculosis, 257
Hemorrhage in emphysematous bulla, 742
Hemorrhage, pulmonary, in tuberculosis, Pneumonectomy for, 426
HENTEL, WILLIAM, AND SHEFTS, LAWRENCE M. Bronchogenic carcinoma and pulmonary tuberculosis, 369
HEPPLESTON, A. G. *See* LURIE, MAX B., *et al.*
HERBUT, PETER A., AND CLERF, LOUIS H. The value of cytological diagnosis of pulmonary malignancy, 60
HILTZ, D. M. *See* MACRAE, D. M., *et al.*
HINSHAW, H. CORWIN, AND MCDERMOTT, WALSH. Thiosemicarbazone therapy of tuberculosis in humans (Report to American Trudeau Society), 145
Histoplasmin, Sensitivity to (letters to the editors), 269
HYDE, BERNARD, AND HYDE, LEROY. Spontaneous mediastinal emphysema and bilateral spontaneous pneumothoraces (case report), 883
——, LEROY, AND HYDE, BERNARD. Spontaneous mediastinal emphysema and bilateral spontaneous pneumothoraces (case report), 883

IBRAHIM, ABDULLA. *See* YOUMANS, GUY P., *et al.*
Infant, 19-day-old, Widespread pulmonary tuberculosis in, Promizole and streptomycin in, 747
Infection, airborne, quantitative, Evaluation of method of, and its use in the study of pathogenesis of tuberculosis, 765
—— in emphysematous bulla, 742
——, tuberculous, airborne, Evaluation of method of, and its use in study of pathogenesis of tuberculosis, 765
——, ——, airborne, in rabbits, 765
——, ——, with streptomycin-resistant organisms, 881
Injections, tuberculin, intravenous, Effect of, on subsequent tuberculin skin reactions in hypersensitive rabbits, 556
Intestinal tuberculosis. *See* Tuberculosis.
In vitro, simple primary amines, 407
In vivo, simple primary amines, 407
Iron, Distribution of, in tuberculous granulation tissue, 560

JENNINGS, A. R., AND SOLTYS, M. A. The dissemination of tubercle bacilli in

experimental tuberculosis in the guinea pig, 399

JOHNSON, BERKLEY H. Plate method for the determination of streptomycin sensitivities of *Mycobacterium tuberculosis*, 578

JONES, EDNA M., PECK, W. M., WOODRUFF, C. E., AND WILLIS, H. S. Relationships between tuberculosis and bronchiectasis. A study of clinical and of postmortem material, 387

——, RUSSELL S., BLACK, THOMAS C., AND SPARR, HAROLD A. Incidence and significance of thromboembolism in pulmonary tuberculosis, 826

KAHN, MARCEL. Primary coccidioidomycosis and concomitant tuberculosis (case report), 887

KÄLLQVIST, IVAR. Para-aminosalicylic acid therapy in intestinal tuberculosis, 621

KATZ, HARRY L. The occurrence of pulmonary tuberculosis following pulmonary excision for nontuberculous disease, 835

——, JULIUS, AND PLUNKETT, ROBERT E. Prevalence of clinically significant pulmonary tuberculosis among inmates of New York State penal institutions, 51

KELLY, RUBY G., AND WOODRUFF, C. EUGENE. Sensitivity to histoplasmin (letters to the editors), 269

KENDIG, EDWIN L., JR., AND ANGELL, FRANKLIN L. Streptomycin and Promizole in the treatment of widespread pulmonary tuberculosis in a 19-day-old infant (case report), 747

KENNEDY, B. R. *See* YERUSHALMY, J., *et al.*

KIRMSE, THOMAS W., AND LINCOLN, EDITH M. Streptomycin-promizole therapy of miliary and meningeal tuberculosis in children, 159

KIRSCHNER, PAUL A., AND WYLIE, ROBERT H. FRIEDLÄNDER'S pneumonia, 465

Kojic acid as inhibitor of tubercle bacilli, 739

KNUDSON, JACK R., AND MITCHELL, ROGER S. The results of the treatment of active minimal pulmonary tuberculosis with "modified" bed rest. A statistical analysis of 289 patients followed for seven years after discharge from Trudeau Sanatorium, 809

KROSS, ISIDOR. Tuberculoma of the lung, simulating bronchogenic carcinoma (case report), 431

LANG, LEONARD P. *See* MOTLEY, HURLEY L., *et al.*

LATTIMER, JOHN K., AMBERSON, J. BURNS, AND BRAHAM, STANLEY. The streptomycin treatment of genitourinary tuberculosis, 518

LEE, HENRY F., BOLTJES, BEN, AND EISENMAN, WILLIAM. Kojic acid as an inhibitor of tubercle bacilli, 738

LEES, WILLIAM M., AND YANG, STEPHEN C. H. Spread or exacerbation of pulmonary tuberculous lesions as a result of thoracoplasty, 648

LEFEBER, EDWARD J., AND RIGDON R. H. Thrombosis of cerebral vessels with necrosis of the basal nuclei. A complication of tuberculous meningitis and streptomycin therapy, 247

LEINER, GEORGE C. *See* STEINBACH, M. MAXIM, *et al.*

Lesion, tuberculous, Effect of streptomycin on morphology of, 525

Lesions, pulmonary tuberculous, Spread of, as result of thoracoplasty, 648

——, vascular, in tuberculous meningitis, 247

LETTERS TO THE EDITORS:

Contagiousness of coccidioidomycosis, 441

Effect of antihistamine medication on the tuberculin reaction, 442

Enzymatic characteristics of suspensions of different mycobacteria, 270

Pulmonary coccidioidomycosis, 158

Sensitivity to histoplasmin, 269

Serum gamma-globulins in pulmonary tuberculosis, 893

LEWIS, W. G., AND ARANY, L. S. Tuberculous infection with streptomycin-resistant organisms (case report), 881

LINCOLN, EDITH M., AND KIRMSE, THOMAS W. Streptomycin-Promizole therapy of miliary and meningeal tuberculosis in children, 159

LINEBERRY, WILLIAM T., JR., AND RYAN, Thomas C. Pneumonectomy for pulmonary hemorrhage in tuberculosis (case report), 426

LOOMIS, RUSSELL N. *See* BOGEN, EMIL, *et al.*

Lucite plombage. *See* Plombage.

Lung abscess, acute, 474
LURIE, MAX B., HEPPLESTON, A. G., ABRAMSON, SAMUEL, AND SWARTZ, IRENE B. An evaluation of the method of quantitative airborne infection and its use in the study of the pathogenesis of tuberculosis, 765

MACRAE, D. M., HILTZ, J. E., AND QUINLAN, J. J., Bronchoscopy in a sanatorium. A review of 522 consecutive bronchoscopies, 355
MAHON, HUGH W. Pathology of pulmonary tuberculosis: As modified by streptomycin therapy, 543
MAJOR, JAMES W., AND BLOOMER, WILLIAM E. The effect of penicillin on wound infection and other complications after thoracoplasty, 346
Malignancy, pulmonary, cytological diagnosis of, 60
MCDERMOTT, WALSH, AND HINSHAW, H. CORWIN. Thiosemicarbazone therapy of tuberculosis in humans (Report to American Trudeau Society), 145
MCPHEE, HARRY R. Miliary tuberculosis (case report), 138
Meningeal tuberculosis. *See* Tuberculosis.
Meningitis, tuberculous, Complication of, and streptomycin therapy, 247
—, —, Effect of streptomycin on the pathology of, 171
—, —, Specific therapy for (editorial), 263
—, —, Vascular lesions in, 247
MERTENS, ANTON, AND BUNGE, ROLF. The present status of the chemotherapy of tuberculosis with Conteben, a substance of the thiosemicarbazone series, 20
MIETZSCH, FRITZ. *See* BEHNISCH, ROBERT, *et al.*
Miliary tuberculosis. *See* Tuberculosis.
Military patients, tuberculous, Air evacuation of, 678
Miners, coal, with pulmonary complaints, Respiratory gas exchange in, 201
Minimal tuberculosis. *See* Tuberculosis.
MITCHELL, ROGER S., AND KNUDSON, JACK R. The results of the treatment of active minimal pulmonary tuberculosis with "modified" bed rest. A statistical analysis of 289 patients followed for seven years after discharge from Trudeau Sanatorium, 809
MOORMAN, LEWIS J. Tuberculosis on the Navaho reservation (editorial), 586
Morbidity rates from tuberculosis, 39
Mortality rates from tuberculosis, 39
MOTLEY, HURLEY L., LANG, LEONARD P., AND GORDON, BURGESS. Studies on the respiratory gas exchange in one hundred anthracite coal miners with pulmonary complaints, 201
MOYER, JOHN H. Pulmonary alveolar adenomatosis (case report), 131
—, AND ACKERMAN, ALFRED J. Sarcoidosis: A clinical and roentgenological study of twenty-eight cases, 299
—, R. E. *See* SCHWARTZ, W. S., *et al.*
Mycobacteria, Enzymatic characteristics of suspensions of (letters to the editors), 270
Mycobacterium tuberculosis, Plate method for determination of streptomycin sensitivities of, 578
M. tuberculosis, Constituents of, 798
—, Resistance of, to drugs, 483
—, Streptomycin sensitivity of, 705
Mycoses, pulmonary, Laboratory diagnosis of, 690

Navaho reservation, Tuberculosis on (editorial), 586
Necrosis of basal nuclei in thrombosis of cerebral vessels, 247
NEPTUNE, WILFRED B., AND BUCKLES, MAURICE G. Tuberculous bronchitis in pulmonary resection, 185
Nodes, sarcoid lymph, Effects of products of, on tubercle bacillus, 730

OWEN, CORA RUST, ADCOCK, JOHN, STOW, ROBERT M., STAUDT, LOUIS W., AND DAVEY, WINTHROP N. Susceptible, resistant, and dependent tubercle bacilli isolated from patients treated with streptomycin, 705
—, GEORGE C. *See* WEISEL, WILSON, *et al.*

PALMER, EDDY D. Tuberculosis of the stomach and the stomach in tuberculosis. A review with particular reference to gross pathology and gastroscopic diagnosis, 116
Para-aminosalicylic acid, Febrile reactions to, 643

Para-aminosalicylic acid in intestinal tuberculosis, 621
—— —— plasma concentrations, Influence of *p*-(Di-n-Propylsulfamyl)-benzoic acid on, 862
—— —— in pulmonary tuberculosis, 597
—— —— (PAS) in pulmonary and extrapulmonary tuberculosis, 613
—— —— for tuberculosis, 226
Paralysis, phrenic, for pulmonary tuberculosis, Pneumoperiteoneum with, 323
Pathology of tuberculous meningitis, Effect of streptomycin on, 171
p-(Di-n-Propylsulfamyl)-benzoic acid, "Benemid," Influence of, on para-aminosalicylic acid (PAS) plasma concentrations, 862
PECK, W. M. *See* JONES, EDNA M., *et al.*
Penal institutions, Prevalence of pulmonary tuberculosis in, 51
Penicillin in wound infection after thoracoplasy, 346
PITTS, FORREST W., AND BOGER, WILLIAM P. Influence of *p*-(Di-n-Propylsulfamyl)-benzoic acid, "Benemid," on para-aminosalicylic acid (PAS) plasma concentrations, 862
Plombage, Lucite, Fatal asphyxia from, 422
PLUNKETT, ROBERT E., AND KATZ, JULIUS. Prevalence of clinically significant pulmonary tuberculosis among New York State penal institutions, 51
Pneumonectomy for pulmonary hemorrhage in tuberculosis, 426
Pneumonia, Friedländer's, 465
Pneumoperitoneum, Appendicitis during, 353
——, Electrocardiogram in, 335
—— with phrenic paralysis for pulmonary tuberculosis, 323
Pneumothoraces, spontaneous, bilateral, and spontaneous mediastinal emphysema, 883
POLACHEK, ABRAHAM, A. *See* STEINBACH, M. MAXIM, *et al.*
Promizole and streptomycin in pulmonary tuberculosis in 19-day-old infant, 747
Promizole-streptomycin. *See* Streptomycin.
Pulmonary adenomatosis. *See* Adenomatosis.
—— coccidioidomycosis. *See* Coccidioidomycosis.
—— hemorrhage. *See* Hemorrhage.
—— malignancy. *See* Malignancy.
—— mycoses. *See* Mycoses.
Pulmonary resection. *See* Resection.
—— tuberculosis. *See* Tuberculosis.

QUINLAN, J. J. *See* MACRAE, D. M., *et al.*

Rabbits, hypersensitive, Effect of intravenous tuberculin injections on subsequent tuberculin skin reactions in, 556
Radiography, mass, Role of dual reading in, 443
RAINE, FORRESTER. *See* WEISEL, WILSON, *et al.*
REISER, HOWARD G., AND HABEEB, WILLIAM J. Pneumoperitoneum with phrenic paralysis for pulmonary tuberculosis, 323
Renal tuberculosis. *See* Tuberculosis.
Resection, pulmonary, Tuberculous bronchitis in, 185
Respiratory gas exchange in anthracite coal miners with pulmonary complaints, 201
RIGDON, R. H., AND LEFEBER, EDWARD J. Thrombosis of cerebral vessels with necrosis of the basal nuclei. A complication of tuberculous meningitis and streptomycin therapy, 247
ROBERTS, E. GWYN, WALLACE, JACK L., AND ERLICH, HENRY. Methods for isolating tubercle bacilli, 563
Roentgenograms, Duplication of, by artificial solarization, 725
ROGERS, ARTHUR E. T., AND DAVIN, JULIA R. Febrile reactions to para-aminosalicylic acid, 643
ROPER, WILLIAM H. Duplication of roentgenograms by artificial solarization: With emphasis on a simple standardized technique, 725
——, AND WARING, JAMES J. Air evacuation of tuberculous military patients, 678
ROSENTHAL, SOL ROY. Bacteriostatic and bactericidal effects of products of sarcoid lymph nodes on the tubercle bacillus, 730
——, AND ELMORE, FRANCIS H. Studies on the contagiousness of coccidioidomycosis:
II. The fate of spherules in sputum exposed out of doors, 95
III. Infection in guinea pigs by contact with diseased animals, 106
RYAN, THOMAS C., AND LINEBERRY, WILLIAM T., JR. Pneumonectomy for pul-

monary hemorrhage in tuberculosis (case report), 426

SANDAGE, CURTIS, AND BIRKELAND, JORGEN M. Effect of intravenous tuberculin injections on subsequent tuberculin skin reactions in hypersensitive rabbits, 556

Sarcoid, Boeck's, 730

—— lymph nodes. *See* Nodes.

Sarcoidosis, 299

SCHAFF, BURNETT, AND BORNSTEIN, SIEGBERT. Appendicitis during pneumoperitoneum treatment, 353

SCHMIDT, HANS: *See* BEHNISCH, ROBERT, *et al.*

SCHWARTZ, W. S., WALTON, S. T., AND MOYER, R. E. Aureomycin in the treatment of tuberculosis, 875

Sensitivity to histoplasmin (letters to the editors), 269

Serosal surfaces, Tuberculosis of, 845

SEYBOLD, WILLIAM D. *See* HEDBURG, GUSTAF A., *et al.*

SHEEHY, JOHN J., AND GUNN, F. D. Experimental tuberculosis in the dog. Comparison of lesions in puppies and in mature dogs, 77

SHEFTS, LAWRENCE M., AND HENTEL, WILLIAM. Bronchogenic carcinoma and pulmonary tuberculosis, 369

SILVERMAN, GERTRUDE, AND SILVERTHORNE, M. CLARE. The effect of streptomycin on the morphology of the tuberculous lesion, 525

——, IRVING, AND FRIEDMAN, ELI. The effect of antihistamine medication on the tuberculin reaction (letters to the editors), 442

SILVERTHORNE, M. CLARE, AND SILVERMAN, GERTRUDE. The effect of streptomycin on the morphology of the tuberculous lesion, 525

SLOTNIK, IRVIN, AND WEISEL, WILSON. Emphysematous bulla complicated by hemorrhage and infection: Treated with surgical drainage (case report), 742

SMALL, MAURICE J. Serum gamma-globulins in pulmonary tuberculosis (letters to the editors), 893

Solarization, artificial, Duplication of roentgenograms by, 725

SOLTYS, M. A., AND JENNINGS, A. R. The dissemination of tubercle bacilli in experimental tuberculosis in the guinea pig, 399

SPARR, HAROLD A. *See* JONES, RUSSELL S., *et al.*

Spirometer, aneroid, Comparison of, with water spirometer, 582

——, water, Comparison of, with aneroid spirometer, 582

SPORER, ANDREW, AND GREENBERGER, MONROE E. Experimental studies on the pathogenesis and prognosis of renal tuberculosis, 508

Spread or exacerbation of pulmonary tuberculous lesions as result of thoracoplasty, 648

STAUDT, LOUIS W. *See* OWEN, CORA RUST, *et al.*

STEINBACH, M. MAXIM, LEINER, GEORGE C., POLACHEK, ABRAHAM, A., AND HELLER, PAUL. Tuberculous patients two and a half years after streptomycin, 868

Stomach, Tuberculosis of, 116

STONE, WILLIAM F., JR., AND GEEVER, ERVING F. Fatal asphyxia as a complication of Lucite plombage (case report), 422

STOW, ROBERT M. *See* OWEN, CORA RUST, *et al.*

Streptomycin Effect of, on morphology of tuberculous lesion, 525

——, —— —— —— pathology of tuberculous meningitis, 171

—— in genitourinary tuberculosis, 518

——, Histopathologic changes in lungs after, 543

——-Promizole in miliary and meningeal tuberculosis in children, 159

—— —— —— in pulmonary tuberculosis in 19-day-old infant, 747

——-resistant organisms, Tuberculous infection with, 881

—— tubercle bacilli, 719

—— sensitivity of *M. tuberculosis*, 705

—— —— of *M. tuberculosis*, 578

——, —— of tubercle bacilli to, 569

—— in tuberculous meningitis, 247

——, Tuberculous patients two and a half years after, 868

SWARTZ, IRENE B. *See* LURIE, MAX B., *et al.*

SWEANY, HENRY C. *See* YOUMANS, GUY P., *et al.*

——, JOAN. *See* YOUMANS, GUY P., *et al.*

THERAPEUTIC TRIALS COMMITTEE OF THE SWEDISH NATIONAL ASSOCIATION AGAINST TUBERCULOSIS. Para-aminosalicylic acid treatment in pulmonary

tuberculosis. Comparison between 94 treated and 82 untreated cases, 597
Thiosemicarbazones, antituberculous activity of, 1, 8
——, Antituberculous activity of, *in vitro* and *in vivo*, 8
——, Chemical studies on, 1
——, Chemotherapy of tuberculosis with, 20
—— in tuberculosis in humans, 145
Thoracoplasty, Effect of penicillin on wound infection after, 346
—— patients, Postoperative management of, 57
——, Spread or exacerbation of pulmonary tuberculous lesions as result of, 648
Thoracoplasties, Use of gelatin foam in, 193
Thromboembolism, Incidence and significance of, in pulmonary tuberculosis, 826
Thrombosis of cerebral vessels with necrosis of the basal nuclei, 247
Tissue, tuberculous granulation, Distribution of iron in, 560
Tubercle bacilli. *See* Bacilli.
Tubercle bacillus. *See* Bacillus.
Tuberculin injections, intravenous, Effect of, on subsequent tuberculin skin reactions in hypersensitive rabbits, 556
—— reaction, Effect of antihistamine on (letters to the editors), 442
—— ——, Effect of antihistaminic drugs upon, 735
—— skin reactions, Acceleration of, 556
Tuberculoma of the lung, simulating bronchogenic carcinoma, 431
Tuberculosis, Aureomycin in treatment of, 875
—— and bronchiectasis, Relationship between, 387
—— chemotherapy, 407
——, —— of, with Conteben, 20
—— and coccidioidomycosis, 887
——, Evaluation of method of quantitative airborne infection and its use in the study of pathogenesis of, 765
——, experimental, Dissemination of tubercle bacilli in, 399
——, ——, in dogs, 77
——, extrapulmonary and pulmonary, Para-aminosalicylic acid in, 613
——, gastric, 116
——, genitourinary, Streptomycin treatment of, 518
——, Implications of changing morbidity and mortality rates from, 39
Tuberculosis, intestinal, Para-aminosalicylic acid therapy in, 621
——, meningeal, in children, Streptomycin-Promizole therapy for, 159
——, miliary, 138
——, ——, in children, Streptomycin-Promizole therapy for, 159
——, pericardial, 845
——, peritoneal, 845
——, pleural, 845
——, Para-aminosalicylic acid for, 226
——, Pulmonary hemorrhage in, Pneumonectomy for, 426
——, ——, active, minimal, Bed rest, "modified," in, 809
——, ——, and bronchogenic carcinoma, 369
——, ——, among New York State penal institutions, 51
——, —— —— extrapulmonary, Para-aminosalicylic acid in, 613
——, pulmonary, following pulmonary excision for nontuberculous disease, 835
——, ——, Incidence and significance of thromboembolism in, 826
——, ——, Para-aminosalicylic acid treatment in, 597
——, ——, Pathology of, 543
——, ——, Pneumoperitoneum with phrenic paralysis for, 323
——, ——, Serum gamma-globulins in (letters to the editors), 893
——, ——, widespread, in 19-day-old infant, Promizole and streptomycin in, 747
——, renal, Experimental studies on pathogenesis and prognosis of, 508
——, Scientific appraisement of new drugs in (editorial), 751
—— of serosal surfaces, 845
—— —— the stomach, 116
—— therapy, rapidly effective, Implications of (editorial), 892
Tuberculous bronchitis. *See* Bronchitis.
—— empyema. *See* Empyema.
—— infection. *See* Infection.
—— lesion. *See* Lesion.
—— meningitis. *See* Meningitis.

VANDERLINDE, ROBERT J., AND YEGIAN, DIRAN. The resistance of tubercle bacilli to chemotherapeutic agents, 483

WALLACE, JACK L. *See* ROBERTS, E. GWYN, *et al.*
WALTON, S. T. *See* SCHWARTZ, W. S., *et al.*

WARING, JAMES J., AND ROPER, WILLIAM H. Air evacuation of tuberculous military patients, 678

WATSON, DENNIS W., AND HECKLY, ROBERT J. Extraction of proteins and other constituents from the tubercle bacillus, with some observations on their chemical and biological properties, 798

WEISEL, WILSON, RAINE, FORRESTER, AND OWEN, GEORGE C. Acute lung abscess, 474

———, AND SLOTNIK, IRVIN. Emphysematous bulla complicated by hemorrhage and infection: Treated with surgical drainage (case report), 742

WILL, DRAKE W. *See* BOGEN, EMIL, *et al.*

WILLIS, H. S. *See* JONES, EDNA M., *et al.*

WINTER, WILLIAM J. The effect of streptomycin upon the pathology of tuberculous meningitis, 171

WOODRUFF, C. EUGENE, AND KELLY, RUBY G. Sensitivity to histoplasmin (letters to the editors), 269

WOODRUFF C. EUGENE. *See* JONES, EDNA M., *et al.*

WYLIE, ROBERT H., AND KIRSCHNER, PAUL A. Friedländer's pneumonia, 465

YANG, STEPHEN C. H., AND LEES, WILLIAM M. Spread or exacerbation of pulmonary tuberculous lesions as a result of thoracoplasty, 648

YEGIAN, DIRAN, AND VANDERLINDE, ROBERT J. The resistance of tubercle bacilli to chemotherapeutic agents, 483

YERUSHALMY, J., HARKNESS, J. T., COPE, J. H., AND KENNEDY, B. R. The role of dual reading in mass radiography, 443

YOUMANS, GUY P., AND DOUB, LEONARD. Studies in tuberculosis chemotherapy. I. Simple primary amines, *in vitro* and *in vivo*, 407

——, IBRAHIM, ABDULLA, SWEANY, JOAN, AND SWEANY, HENRY C. A direct method for the determination of the sensitivity of tubercle bacilli to streptomycin, 569

LIST OF JOURNALS ABSTRACTED

Acta pathologica et microbiologica Scandinavica
Acta tuberculosea Scandinavica
American Heart Journal
American Journal of Clinical Pathology
American Journal of Hygiene
American Journal of the Medical Sciences
American Journal of Medicine
American Journal of Physiology
American Journal of Roentgenology and Radium Therapy
Annales de l'Institut Pasteur
Annals of Allergy
Annals of Western Medicine and Surgery
Archives of Disease in Childhood
Archives of Internal Medicine
Archives of Pediatrics

Beitrage zur Klinik der Tuberkulose
British Journal of Pharmacology and Chemotherapy
British Journal of Radiology
British Medical Journal
Bulletin of the Johns Hopkins Hospital

Chinese Medical Journal
Clinica tisiologica

Diseases of the Chest

Giornale italiano della tuberculosi

Hoja tisiológica

Industrial Hygiene and Toxicology
Industrial Medicine and Surgery

Journal of the American Medical Association
Journal of the American Veterinary Medical Association
Journal of Bacteriology
Journal of Clinical Investigation
Journal of Infectious Diseases
Journal of Laboratory and Clinical Medicine
Journal Lancet
Journal of the Medical Association of Israel
Journal of the National Medical Association
Journal of Pathology and Bacteriology
Journal of Thoracic Surgery
Journal of Pharmacology and Experimental Therapeutics

Lancet
Lékarske listy
Lotta contro la tuberculosi

Medical Clinics of North America
Medical Journal of Australia

New England Journal of Medicine

Poumon
Presse médicale
Problemy tuberkuleza
Proceedings of the Society for Experimental Biology and Medicine
Public Health Reports

Quarterly Bulletin of Sea View Hospital
Quarterly Journal of Medicine

Radiology
Revista brasileira de tuberculose
Revista mexicana de tuberculosis
Revista Panamerican de Medicina and chirurgica Tor
Revue de la Tuberculose
Rozhledy v tuberculosea

Schweizerische medizinische Wochenschrift
Schweizerische Zeitschrift für Tuberculose

Semaine des Hopitaux
Surgery, Gynecology and Obstetrics

Tegen de Tuberculose
Thorax
Tubercle
Tuberculoseartz

Wiener klinische Wochenschrift

INDEX OF ABSTRACTS

Clinical Studies, Tuberculosis
1-7, 29-32, 49-52, 69-71, 85-88

Clinical Studies, Nontuberculous Diseases
7-19, 32-37, 52-59, 71-78, 88-95

Antimicrobial Therapy
19-24, 37-40, 59-63, 78-82, 95-99

Laboratory Studies
25-27, 40-46, 63-67, 82-83, 99-102

Public Health and Epidemiology
27-28, 46-48, 67-68, 83-84, 102-104

Ablard. *See* Duroux, A., *et al.*
Abreu, M. de. New types of tomography, 32
Abscess, lung, Resection for, 16
——, pulmonary, acute, 35
——, ——, treatment of, 12
——, tuberculous, 96
Absorption, pulmonary, 62
Acclimatization, respiratory, to altitude, 42
Acid, para-aminosalicylic, Effect of, 22
——, Usnic, derivatives, 23
Acid-fast bacilli. *See* Bacilli.
Adams, H. Esophageal diverticula, 13
——, W., and Kershner, R. Chronic nonspecific pneumonitis, 10
——, W. L. *See* Campbell, G. S., *et al.*
——. *See* Haddy, F. J., *et al.*
Adelsberger, L. *See* Rubin, E. H., *et al.*
Adenitis, Roentgen therapy of, 70
Adenomatosis, pulmonary, 35, 76
Adenopathy, mediastinal, tuberculous, 49
Adhesions, pleural, 77
Adults, Minimal tuberculosis in, 46
Aerosol PAS for tuberculosis, 81
——, Surface-active agents via, 39
Agents, surface-active, via aerosol, 39
Agranulocytosis with thiosemicarbazone, 79
Air, alveolar, 41
—— embolism, arterial, 74
Airborne tuberculosis. *See* Tuberculosis.
Alexander, H. L., Flance, I. J., *et al.* Pleural mesothelioma, 36
Alfero, M. Pleural adhesions, 77
Allen, T. C. *See* Shepard, K. S., *et al.*
Allison, P. R. Pulmonary cysts, 14
——, S. T., Volk, R., and Vitagliano, G. R. Dihydrostreptomycin for pulmonary tuberculosis, 19
Alström, C.-H., Gentz, C., and Lindblom, K. Schizophrenia and tuberculosis, 2
Altitude, Respiratory acclimatization to, 42
Alveolar air, 41
Alvim, A. C., and Nasciemento, E. A. do. Streptomycin sensitivity, 22
Amidase of tuberculous tissue, 100
Aminophylline, micronized, for asthma, 12
Ammonium pulmonary edema, 43
Anderson, D. A. Tuberculous empyema, 29
Anemia due to thiosemicarbazone, 79
Aneurysm, Differentiation of mediastinal tumor and, 77
——, Ductus arteriosus, 76
—— of phrenic vessels, 94
Angelman, H., and Turner, W. M. L. Intratracheal rupture of tuberculous lymph node, 69
Angiocardiography, 19, 78
Anoxia during surgery, 18
Antibiotics against *M. tuberculosis*, 97
Antihistaminic drugs for tuberculosis, 3
Antihistaminics and tuberculosis, 86
Appel, M., and Bronk, T. T. Tumor cells in bronchial secretions, 40
Arismendi, L., and Duisenberg, C. E. Pulmonary arteriovenous fistula, 16
Arnes, W. H., and Raffel, S. Tuberculo-complement-fixation in sarcoidosis, 72
Arterio-sclerosis, pulmonary, 33
Arteriovenous fistula, 58, 94
Artery, anomalous pulmonary, 93
Arthritis, rheumatoid, Lung lesions in, 11
Aspergillosis, pulmonary, 55
Aspiration, needle, in lung cancer, 36
Assis, A. de. BCG vaccination in Brazil, 46
Asthma, bronchial, Orthoxine in, 56
——, micronized aminophylline for, 12
——, Sympathectomy for, 13
Atelectasis, postoperative, Treatment of, 36
Atomization, penicillin, Intratracheal, 81

Atypical pneumonia. *See* Pneumonia.
Aureomycin for atypical pneumonia, 98
—— —— pulmonary changes in pancreatic fibrosis, 24
—— in treatment of experimental tuberculosis, 98
Autogenous bone pegs in ribs, 5
Avian bacillus. *See* Bacillus.
—— tuberculosis. *See* Tuberculosis

Baarsma, P., Dirken, M., and Huizinga, E. Collateral intralobar ventilation, 26
Bacilli, acid-fast, Concentration of, 45
——, ——, Demonstration of, in sputum, 66
Bacillus, avian, Variant of, 45
Bacilli, tubercle, Growth of, 63
——, ——, —— inhibition of, 64
——, ——, —— of, and riboflavin, 26
——, ——, Rate of growth of, 64
——, ——, Staining of, 82
——, ——, streptomycin-dependent, 61
——, ——, —— -resistant, Transmission of, 61
——, ——, —— sensitivity of, 81
——, ——, Virulence of, 100
Bacterial Metabolism. *See* Metabolism.
Bactericidal action of trithylene glycol, 67
Bagnall, D. J. T., and Dunner, L. Pneumoconiosis in graphite workers, 75
Bailey, C. P., Glover, R. P., and O'Neill, T. J. E. Streptomycin and resections, 21
Balozet, P. *See* Mattei, Ch., *et al.*
Barach, A. L., and Eastlake, C., Jr. PAS for tuberculosis, 21
Basal-cell metastases. *See* Metastases.
Bass, H. E., Schomer, A., and Berke, R. Residual coccidioidomycotic lung lesions, 8
Bayer, D. *See* Johnson, H., *et al.*
BCG, Hazard of, 104
—— tuberculin test, 103
—— vaccination, 67
—— ——, Apparatus for, 47
—— —— in Brazil, 46
—— —— —— ——, Results of, 84
Beakey, J. F. *See* Gaensler, E. A., *et al.*
Beams, A. J., and Harmos, O. Pulmonary fibrosis, 34
Bean, D. *See* Kergin, F., *et al.*
Beattie, E. J., Jr., Blades, B., and Horton, C. Streptomycin in the pleural cavity, 22
——, M. Cultivation of *M. tuberculosis*, 26
Beck, G. *See* Unger, P., *et al.*
Bentegeat, J. *See* Verger, P., *et al.*
Berard, M. and Juffin, P. Pleural pneumonectomy, 50
Bergqvist, S., and Packalén, T. Hyaluronidase in tuberculosis, 100
Berke, R. *See* Bass, H. E., *et al.*
Bernard, E., Kreis, B. Lotte, A., Chiche, P., and Paley, P. V. Streptomycin for tuberculous meningitis, 79
Berseus, S. *See* Werko, L., *et al.*
Berthet, J. G., and Rossel, G. Fluid motion in hydropneumothorax, 6
Bertrand, L. *See* Janbon, M., *et al.*
Berylliosis, nonoccupational, 54
Beryllium determinations, Value of, 33
—— granulomatosis, chronic, 32
Bethlem, N. Streptomycin therapy, 59
Bierman, H. R., and Shimkin, M. B. Chemotherapy of neoplastic disease, 98
Billings, J. H., and Freedman, E. Active bronchopulmonary lithiasis, 90
Binford, C. H. *See* Gledhill, E. Y., *et al.*
Biopsy, liver, 69
——, ——, in tuberculosis, 50
Birkhaug, K. Apparatus for BCG vaccination, 47
Birsner, J. W., and Smale, L. E. Obstetrical coccidioidomycosis, 55
Blades, B. *See* Beattie, E. J., Jr. *et al.*
Bland, E. F., and Sweet, R. H. Shunt for mitral stenosis, 57
Blind, P. *See* Sarroste, J., *et al.*
Blood concentration of thiosemicarbazones, 39
—— elements and pneumothorax, 83
——, intrapleural, Incoagulability of, 83
Blumberg, N. *See* Gouley, B. A., *et al.*
Blumenfeld, H., and Grayson, C. E. Egg shell calcifications in silicosis, 89
Bøe, J. Possible hazard of BCG, 104
Boiteux, M. *See* Kourilsky, R., *et al.*
Bolivia, Tuberculosis in, 27
Bone and joint tuberculosis, Surgery in, 52
—— marrow, Phagocytic activity of, 82
—— pegs, autogenous, in ribs, 5
Botelho, G., and Fleury de Amorin, D. Cavernous hemangioma in the lung, 76
Bottinelli, M. D. *See* Ferrar, M., *et al.*
Boucher, Y. le. *See* Kourilsky, R., *et al.*
Boulaud, E., and Solomidès, J. PAS in experimental tuberculosis, 62
Boxer, G. E., Jelinek, V. C., and Edison, A. O. Fate of streptomycin, 95
Brazil, BCG vaccination in, 46
——, Pulmonary brucellosis in, 54
——, Results of BCG vaccination in, 84

Brennan, A. J., and Wichelhausen R. H. Transmission of streptomycin-resistant tubercle bacilli, 61
Brewer, L., III, Jones, W., and Dolley, F. Lesions simulating bronchiogenic carcinoma, 14
Brock, R. C. Valvulotomy for pulmonary stenosis, 57
Bronchial asthma. *See* Asthma.
—— carcinoma. *See* Carcinoma
—— dynamism, 101
—— lavage. *See* Lavage.
—— secretions, Cytohistology of, 41
—— ——, Tumor cells in, 40
Bronchiectasis, 93
——, Pathology of, 18
Bronchiogenic carcinoma, Lesions simulating, 14
Bronchitis, chronic, 73
Bronchodilator, Action of, new, 102
Bronchopulmonary infections. *See* infections
—— lithiasis, active, 90
—— moniliasis. *See* Moniliasis
Bronchospirometry, 86
Bronchus, Fracture of, 37
Bronk, T. T., and Appel, M. Tumor cells in bronchial secretions, 40
Brown, C. J. Resection for tuberculosis, 5
Brucellosis, pulmonary, in Brazil, 54
Bubis, S., and Erwin, J. H. Pulmonary adenomatosis, 35
Budd, V. *See* Yegian, D., *et al.*
Burch, J. *See* Johnson, H., *et al.*
Burchell, H. B. *See* Edwards, J. E., *et al.*
Burnip, R., and Cohen, R. Miliary coccidioidomycosis in a child, 89
Bustamente, O. S. de. *See* Farinas, P. L., *et al.*

Cain, J. C. Epidemic pulmonary disease, 7
Calcifications, egg shell, in silicosis, 89
—— in histoplasmosis, 90
——, pulmonary, 102
Campbell, G. S., Haddy, F. J., Adams, W. L., and Visscher, M. B. Pulmonary effects of intracranial pressure, 44
——. *See* Haddy, F. J., *et al.*
Cancer, Bronchial smears in, 16
——, lung, Needle aspiration in, 36
——, ——, Origin of sputum in, 16
Canetti, G., and Saenz, A. Willis phenomenon and streptomycin, 60
Capps, S. C., and Lodmell, E. A. Pneumothorax with metastatic sarcoma, 15
Carbon dioxide inhalation in emphysema, 41
Carcinoma, bronchial, Sputum cytology in, 77
——, bronchiogenic, Lesions simulating, 14
—— of lung, 58
—— from paraffinomas, 92
"Cardiac lung", Surgical treatment of, 57
—— output studies, 27
Carmody, M. G. *See* DeNardi, J. M., *et al.*
Carr, C. E. *See* Morgenstern, P., *et al.*
——, D., and Chandler, H. Sympathectomy for asthma, 13
——, D. T. *See* Karlson, A. G., *et al.*
Carter, R. A. *See* Jacobson, G., *et al.*
Carvalho, A. de. Skin reaction to tuberculin, 47
——. Histoplasmosis in Brazil, 8
——. New uses of kymography, 59
——, DeSousa, A., and Vidal, C. New roentgen kymograph, 6
Castello-Branco, J. M. Endoscopic phrenicectomy, 31
Caubarrere, N. L. *See* Ferrar, M., *et al.*
Cavernostomy and tamponade with PAS, 87
Cavities and streptomycin resistance, 59
——, tuberculous pulmonary, healing of, 86
Cavity, pleural, Streptomycin in, 22
Cazal, P. *See* Janbon, M., *et al.*
Cazier, P. D., and Ruhe, J. S. Histoplasmosis, 7
Cerone, M., and Schwartzman, J. Tuberculin patch tests, 68
Chandler, H., and Carr, D. Sympathectomy for asthma, 13
Chang, N. C. T., and DeFuentes, A. S. Lucite spheres for pulmonary collapse, 51
Chapman, P. *See* Day, J. *et al.*
Chemotherapy of neoplastic disease, 98
Chenebault, J. Pancoast-Tobias syndrome, 92
Chest pathology in infectious mononucleosis, 75
Chest tumors, solitary, 15
Chiche, P. *See* Bernard, E., *et al.*
Child, Avian tuberculosis in, 85
——, Miliary coccidioidomycosis in, 89
Childhood tuberculosis. *See* Tuberculosis.
—— ——, Streptomycin for, 38
Children, Chloromycetin for pneumonia in, 81
——, Coccidioidomycosis in, 55
Chloromycetin for pneumonia in children, 81
——, Tuberculostatic action of, 23
Cholak, J. *See* Dutra, F. R., *et al.*
Cholesterol pneumonitis, chronic, 88
Chrest, C. P. *See* Lampe, I., *et al.*
Christensen, N. A. *See* Edwards, J. E., *et al.*
Ciosi-Frenay. *See* Sarroste, J., *et al.*
Circulation, Effect of artificial respiration on, 27

Circulation in emphysema, 56
—— and respiration, 44
Clagett, O. T. *See* McDonald, J. R., *et al.*
Clark, M., and Ricker, W. Sarcoidosis, 71
Cleland, W. P. Extrapleural pneumonolysis, 4
Coccidioidomycosis in children, 55
——, miliary, in a child, 89
——, obstetrical, 55
——, pulmonary, surgical, 35
Coccidioidomycotic lung lesions, 8
Cohen, R. Coccidioidomycosis in children, 55
——, and Burnip, R. Miliary coccidioidomycosis in a child, 89
Cohn, B., and Guggenheim, A. Rib fracture after thoracoplasty, 6
Cold prevention, triethylene glycol for, 48
Collapse, pulmonary, Lucite spheres for, 51
——, ——, in pertussis, 11
—— therapy, Results with, 51
Collateral intralobar ventilation, 26
Colleau, A., and Rivoire, R. Streptomycin for tuberculous meningitis, 60
Collins, H. S., Wells, E. B., Gocke, T. M., and Finland, M. Aureomycin for atypical pneumonia, 98
Colon, Fate of streptomycin in, 96
Complex, primary, cutaneous, 1
Concentration of acid-fast bacilli, 45
Concentrations, blood, of thiosemicarbazones, 39
Congenital heart disease. *See* Heart disease.
Congo Red test, 27
Conklin W. S. *See* Richardson, H. L., *et al.*
Cor pulmonale, 34
Corper H. J., and Nelson, C. R. Concentration of acid-fast bacilli, 45
Cosgriff, S. W. Coagulation in hemopneumothorax, 101
Cossio, P., and Perianes, I. Surgical treatment of "cardiac lung", 57
Crane, P., Lerner, H. H., and Lawrence, E. A. Arteriovenous fistula, 58
Craver, L. *See* Watson, W. L., *et al.*
Cregar, W. P. *See* Smith, J. W., *et al.*
Crocker, A. C. *See* Schwachman, H., *et al.*
Crofton, J. Lower lobe tuberculosis, 1
Cromwell, H. *See* Watson, W. L., *et al.*
Crystalline streptomycin, 37
Cummings, M. M. *See* Patnode, R. A., *et al.*
Cviklinsky, S. *See* Lévi-Valensi, A., *et al.*
Cysts, pulmonary, 14
Cytohistology of bronchial secretions, 41
Cytology, sputum, in bronchial carcinoma, 77
Cytolysis, tuberculin, Complement in, 100
—— by tuberculin, Plasma factor in, 82

Dauster, J. *See* Fontes-Magarão, M., *et al.*
Davis, R. H. Streptomycin for tuberculous sinuses, 80
Day, J., Chapman, P., and O'Brien, E. Closed intrapleural pneumonolysis, 3
De S. N. Streptomycin and hydrocephalus, 38
Deane, E. H. W. Pneumothorax in elderly subjects, 31
Decortication of hemopneumothorax, 17
——, postpneumothorax, 4
Decroix, E. *See* Kourilsky, R., *et al.*
Deeb, A. A., and Erfan, H. Pulmonary schistosomiasis, 73
DeFuentes, A. S., and Chang, N. C. T. Lucite spheres for pulmonary collapse, 51
Delaude, A. *See* Karlson, A. G., *et al.*
Delord, M. *See* Le Melletier, J., *et al.*
DeNardi, J. M., Van Ordstrand, H. S., and Carmody, M. G. Chronic beryllium granulomatosis, 32
Denlinger, R. B. *See* Jacobson, G., *et al.*
Des Autels, E. J. *See* Shamaskin, A., *et al.*
DeSousa, A. *See* Carvalho, L. de, *et al.*
Determinations, beryllium, Value of, 33
Diaphragm, elevated, versus fluid, 87
Diaphragmatic hernia, 13
Dickie, H. A., and Grimm, E. Loeffler's syndrome, 74
Dihydrostreptomycin for pulmonary tuberculosis, 19
Diphosgene action on lung, 43
DiRienzo, S. Bronchial dynamism, 101
Dirken, M. *See* Baarsma, P., *et al.*
Disturbances, visual, with streptomycin, 39
Diverticula, esophageal, 13
Doane, E. A., and Furtos, N. C. Transmission of streptomycin-resistant tubercle bacilli, 61
Dolley, F. *See* Brewer, L., III, *et al.*
Dorner, R., and March, D. Primary rib tumors, 15
Dotter, C. T., and Steinberg, I. Angiocardiography, 19
——, and Steinberg, I. Differentiation of mediastinal tumor and aneurysm, 77
Douglas, J. M. *See* Edwards, J. E., *et al.*
Dubois de Montreynaud, J. *See* Meyer, A. *et al.*
Dubos medium with penicillin, 26
Duca, C. J., and Scudi, J. V. Neohetramine in experimental tuberculosis, 25
Ductus arteriosus aneurysm, 76

Dugan, D. J., and Samson, P. S. Traumatic diaphragmatic hernia, 13
Duisenberg, C. E., and Arismendi, L. Pulmonary arteriovenous fistula, 16
Dunner, L., and Bagnall, D. J. T. Pneumoconiosis in graphite workers, 75
Durant, T. M., Oppenheimer, M. J., Webster, M. R., and Long, Joan. Arterial air embolism, 74
Duroux, A., Verges, Marty, Ablard, and Moreau. Streptomycin for pulmonary tuberculosis, 80
Dustan, C. *See* Eisenbud, M., *et al.*
Dutra, F. R., Cholak, J., and Hubbard, D. M. Value of beryllium determinations, 33
Dynamism, bronchial, 101

Eastlake, C., Jr., and Barach, A. L. PAS for tuberculosis, 21
Eberle, A. F. F. Tuberculous, pleural effusion, 2
Eddy, G. S. Pneumonectomy, 5
Edema, pulmonary, ammonium, 43
Edison, A. O. *See* Boxer, G. E., *et al.*
Edwards, J. E., Douglas, J. M., Burchell, H. B., and Christensen, N. A. Intrapulmonary vessels in congenital heart disease, 34
Edwards, L. B. *See* Goddard, J. C., *et al.*
Effects, pulmonary, of intracranial pressure, 44
——, vaccine, on respiration, 43
Effusion, pleural, tuberculous, 2
Eisenbud, M., Wanta, R. C., Dustan, C., Steadman, L. T., Harris, W. B., and Wolf B. S. Nonoccupational berylliosis, 54
Electrocardiograms in sarcoidosis, 92
Electrokymography, 18
Electrophrenic respiration, 11
Elkin, D. C. Aneurysm of phrenic vessels, 94
Elliot, W. Unexplained mortality figures, 48
Ellis, F. A., Grant, R., and Hall, V. E. Vaccine effects on respiration, 43
Elrod, P. and Murphy, J. Decortication of hemopneumothorax, 17
——, P. D. *See* Moore, J. A., *et al.*
Embolism, Arterial air, 74
——, pulmonary, 34
Emmart, E. W., Kissling, R. E., and Stark, T. H. Tuberculostasis with Nocardia extracts, 23
Emmons, C. W. Potential source of histoplasmosis, 90
Emphysema, Circulation in, 56
——, Carbon dioxide inhalation in, 41
—— from tracheal puncture, 56
Empyema, Enzyme treatment of, 12
——, Exploratory thoracotomy in, 17
——, putrid, 62
——, tuberculous, 29, 30
——, ——, TB 1/E for, 78
Eosinophilic pneumonia, 52
—— xanthomatous granuloma, 35
Ephedrin-penicillin inhalation, 40
Epidemic pulmonary disease, 7
Endobronchial occlusion. *See* Occlusion.
Endoscopic phrenicectomy, 31
England, Tuberculosis in, 48
Enzyme treatment of empyema, 12
Erfan, H., and Deeb, A. A. Pulmonary schistosomiasis, 73
Erwin, J. H., and Bubis, S. Pulmonary adenomatosis, 35
Erythema nodosum, 29
Esophageal diverticula, 13
—— hernias. *See* Hernias.
Esperson, E. Growth of tubercle bacilli, 63
Etzel, E. Results with collapse therapy, 51
Evans, W. A., Jr. Respiratory tract obstructions, 58
Extrapleural pneumonolysis. *See* Pneumonolysis.
—— pneumothorax. *See* Pneumothorax.
Experimental tuberculosis. *See* Tuberculosis.
Eye test, rabbit, 22

Fainsinger, M. H., and Oosthuizen, S. F. Hydatid disease, 90
Farinas, P. L., Bustamante, O. S. de, Lott, L. M., and Revuelta, R. Intratracheal penicillin atomization, 81
Favour, C. B. *See* Miller, J. M., *et al.*
——, and Fremont-Smith, P. White cell lysis by tuberculoprotein, 25
Feldman, J. *See* Matos, G. de, *et al.*
——, W. H. *See* Karlson, A. G., *et al.*
——, Hutchinson, D. W., Schwarting, V. M. and Karlson, A. G. Avian tuberculosis in a child, 85
Felson, B., Rosenberg, L. S., and Hamburger, M., Jr. Acute Friedländer's pneumonia, 88
Fernandes, R. Pulmonary brucellosis in Brazil, 54
——. *See* Fontes-Magarão, M., *et al.*
Ferrar, M., Caubarrere, N. L., Bottinelli, M. D., Mendilaharsa, C., and Giudice, D. Diffuse interstitial fibrosis, 89
Fibrosis, cystic, of the pancreas, 11
——, Diffuse interstitial, 89

Fibrosis, pancreatic, Aureomycin for pulmonary changes in, 24
——, pulmonary, 34
Filho, A. MacDowell. Results of BCG vaccination in Brazil, 84
Finland, M. *See* Collins, H. S., *et al.*
Finnegan, J. *See* Yater, W. M., *et al.*
First, S. R. Electrocardiograms in sarcoidosis, 92
Fistula, arteriovenous, 58, 94
——, pulmonary arteriovenous, 16
Flance, I. J. *See* Alexander, H. L., *et al.*
Fleischner, F. G. Bronchial peristalsis, 77
Fleury de Amorim, D., and Botelho, G. Cavernous hemangioma in the lung, 76
Florestano, H. J. New tuberculocidal compounds, 98
Fluid motion in hydropneumothorax, 6
—— versus elevated diaphragm, 87
Foci, round, in childhood tuberculosis, 52
Foley, G. E. *See* Schwachman, H., *et al.*
Fontes-Magarão, M., Fernandes, R., and Dauster, J. Variant of avian bacillus, 45
——, Linhares, H., and Vieira, A. Obstetrical tuberculosis, 29
Forsgren, A. L. Putrid empyema, 63
Fourestier, M. *See* Kourilsky, R., *et al.*
Fracture of bronchus, 37
——, rib, after thoracoplasty, 6
Freedman, E., and Billings, J. H. Active bronchopulmonary lithiasis, 90
Fremont-Smith, P., and Favour, C. B. White cell lysis by tuberculoprotein, 25
Friedlaender, A. S., and Friedlaender, S. Orthoxine in bronchial asthma, 56
——, S., and Friedlaender, A. S. Orthoxine in bronchial asthma, 56
Friedländer's pneumonia, 73
—— ——, acute, 88
Friedman, E., and Silverman, I. BCG tuberculin test, 103
Furcolow, M. L. Calcification in histoplasmosis, 90
Furtos, N. C., and Doane, E. A. Transmission of streptomycin-resistant tubercle bacilli, 61
Fury, L. Bronchospirometry, 86

Gaensler, E. A., Beakey, J. F., and Segal, M. S. Pulmonary absorption, 62
Gardner, G. M. *See* Weiser, R. S., *et al.*
——, P. A., Rees, R. J. W., and Robson, J. M. Rabbit eye test, 22
Gastric specimens, Preservation of, 65
Gentz, C. *See* Alström, C.-H., *et al.*
Gerard, R. W. *See* Tobias, J. M., *et al.*
Gershman, M. Osseous tuberculosis of the hand, 31
Getz, H. R. *See* Koerner, T. A., *et al.*
Giffin, H. M. *See* Yater, W. M., *et al.*
Gigliaccio, A. V. *See* Hager, H. F., *et al.*
Gillanders, A. D. Circulation in emphysema, 56
Gines, A. R. Hydatid disease in Paraguay, 91
Giron, J. *See* Le Melletier, J., *et al.*
Giudice, D. *See* Ferrar, M., *et al.*
Gledhill, E. Y., Sprigg, J. B., and Binford, C. H. Needle aspiration in lung cancer, 36
Gloor, H. U., and Uehlinger, E. Caseating pyelitis, 3
Glover, R. P. *See* Bailey, C. P., *et al.*
Gloyne, S. R., and Heppleston, A. G. Pulmonary aspergillosis, 55
Glycol, triethylene, for cold prevention, 48
Goeke, T. M. *See* Collins, H. S., *et al.*
Goddard, J. C., Edwards, L. B., and Palmer, C. E. Pulmonary calcifications, 102
Góis, P. de. Staining of Much's granules, 82
Goiter, intrathoracic, 14
Golden, R., and Rottenberg, L. A. Spontaneous pneumothorax, 94
Goldstein, P. Emphysema from tracheal puncture, 56
Gorlitzer von Mundy, V. Manganese chloride for tuberculous meningitis, 40
Gauley, B. A., Blumberg, N., and Grayson, R. J. Tuberculous splenomegaly, 2
Graddock, C. G., and Meredith, H. C., Jr. Liver biopsy in miliary tuberculosis, 50
Graessle, O. E., and Pietrowski, J. J. Effect of para-aminosalicylic acid, 22
Graf, K. Streptomycin toxicity, 38
Grant, R. *See* Ellis, F. A., *et al.*
——, W. C. Pneumothorax and blood elements, 83
Granules, Much's, Staining of, 82
Granuloma, eosinophilic, xanthomatous, 35
Granulomatosis, beryllium, chronic, 32
Graphite as cause of pneumoconiosis, 75
—— workers, Pneumoconiosis in, 75
Grayson, C. E. Infarcts in opiate addiction, 56
——, and Blumenfeld, H. Egg shell calcifications in silicosis, 89
Grayson, R. J. *See* Gouley, B. A., *et al.*
Greece, Photofluorographic survey in, 103
Greer, S. J., and Grow, J. B. Surgical pulmonary coccidioidomycosis, 35
Griffith, J. L. Fracture of bronchus, 37

Grimm, E., and Dickie, H. A. Loeffler's syndrome, 74
Grishman, A., Poppel, M. H., Simpson, R. S., and Sussman, M. L. Angiocardiography, 78
Gropper, A. L. *See* Taplin, G. V., *et al.*
Grow, J. B., and Greer, S. J. Surgical pulmonary coccidioidomycosis, 35
Guggenheim, A., and Cohn, B. Rib fracture after thoracoplasty, 6

Haddy, F. J. *See* Campbell, G. S., *et al.*
——, Campbell, G. S., Adams, W. L., and Visscher, M. B. Pulmonary vascular pressures, 45
——, ——, and Visscher, M. B. Lung changes in hyperthermia, 43
Hageman, J. R. *See* Taplin, G. V., *et al.*
Hager, H. F., Gigliaccio, A. V., and Young R. M. Nocardiasis, 33
Hall, V. E. *See* Ellis, F. A., *et al.*
Hamburger, M., Jr. *See* Felson, B., *et al.*
Hamilton, K. A. Spondylarthritis, 37
Hand, Osseous tuberculosis of, 31
Hardenbergh, E. *See* Whittenberger, J., *et al.*
Harmos, O., and Beams, A. J. Pulmonary fibrosis, 34
Harrington, S., and Olsen, A. Esophageal hernias of the short esophagus type, 13
——, S. W. *See* McDonald, J. R., *et al.*
Harris, W. B. *See* Eisenbud, M., *et al.*
Harrison, J. M. Avian tuberculosis, 71
Hässig, A., Karrer, J., and Pusterla, F. Human pseudotuberculosis, 54
Hatfield, W. H., and Hill, J. E. Pulmonary adenomatosis, 76
Hayward, J., and Reid, L. Cavernous pulmonary telangiectasis, 94
Heart disease, congenital, Intrapulmonary vessels in, 34
Heckenroth, M. *See* Le Melletier, J., *et al.*
Hemangioma, cavernous, in the lung, 76
Hemopneumothorax, Coagulation in, 101
——, Decortication of, 17
Hemosiderosis, idiopathic, 9
—— in mitral disease, 10
Henderson, A. R., and Judd, A. R. Antihistaminic drugs for tuberculosis, 3
Heppleston, A. G. Air-borne tuberculosis in the rabbit, 65
——, and Gloyne, S. R. Pulmonary aspergillosis, 55
Herb, C. O., and Konzett, H. Action of new bronchodilator, 102
Hernia, strangulated, and pneumoperitoneum, 31
——, traumatic diaphragmatic, 13
——, Esophageal, of short esophagus type, 13
Hickey, M. D., and Sellars, T. H. Resection for pulmonary tuberculosis, 4
Hilbish, T. F. Small-film screening in major cities, 83
Hill, J. E., and Hatfield, W. H. Pulmonary adenomatosis, 76
Histoplasmosis, 7
——, Calcification in, 90
—— in Brazil, 8
——, Potential source of, 90
Hirsch, E. F., and Tucker, F. C. Nocardiosis, 8, 55
Hodgkin's disease, Sternal marrow in, 91
Hoggarth, E., Martin, A. R., Storey, N. E., and Young, E. H. P. Thiosemicarbazones for tuberculosis, 39
Holman, J., and Shires, G. T. Carbon dioxide inhalation in emphysema, 41
Holt, J. F., and Owens, W. I. Osseous lesions of sarcoidosis, 18
Homma, H. Intrathoracic neurogenic tumors, 36
Horton, C. *See* Beattie, E. J., Jr. *et al.*
Hou, H. C. Riboflavin and growth of tubercle bacilli, 26
Hubbard, D. M. *See* Dutra, F. R., *et al.*
Huizinga, E. *See* Baarsma, P., *et al.*
Humiston, J. *See* Smith, J. W., *et al.*
Hunter, W. C. *See* Richardson, H. L., *et al.*
Hurwitz, A., and Yesner, R. Surgery for bronchopulmonary moniliasis, 16
Hurst, A., and Millner, T. Tuberculosis and antihistaminics, 86
Hutchinson, D. W. *See* Feldman, W. H., *et al.*
Hyaluronidase in tuberculosis, 100
Hydrocephalus and streptomycin, 38
Hydropneumothorax, fluid motion in, 6
Hydatid disease, 90
—— —— in Paraguay, 91
Hypersensitivity, tuberculin, transferred to man, 100
Hyperthermia, Lung changes in, 43

Ibiapina, A., and Neves, A. Pneumoperitoneum for pulmonary tuberculosis, 31
Infarcts in opiate addiction, 56
Infections, bronchopulmonary, 74
Influenza virus in pneumonia, 9
Inhalation, carbon dioxide, in emphysema, 41
——, ephedrin-penicillin, 40

Intracranial pressure. *See* Pressure.
Intrapleural blood, Incoagulability of, 83
—— pneumonolysis. *See* Pneumonolysis.
Intrapulmonary vessels in congenital heart disease, 34
Intratracheal penicillin atomization, 81
Intrathoracic goiter, 14
—— tumors. *See* Tumors.
Irvin, G. E. Cor pulmonale, 34

Jacobson, G., Denlinger, R. B., and Carter, R. A. Q fever pneumonia, 88
Janbon, M., Cazal, P., and Bertrand, L. Liver biopsy, 69
Jelinek, V. C. *See* Boxer, G. E., *et al.*
Jews, Yemenite, Tuberculosis in, 102
Johnson, H., Burch, J., Bayer, D., and McClellan, G. Pregnancy in pulmonary tuberculosis, 1
Jones, M. J., and Tobie, W. C. PAS in bacterial metabolism, 23
——, W. *See* Brewer, L., III, *et al.*
Jorgens, J., and Stauffer, J. Electrokymography, 18
Judd, A. R., and Henderson, A. R. Antihistaminic drugs for tuberculosis, 3
Juffin, P., and Berard, M. Pleural pneumonectomy, 50

Kabler, P., and Lundholm, R. Preservation of gastric specimens, 65
Kahn, R. L. Serologic reaction in tuberculosis, 45
Kaplan, S. R. *See* Shepard, K. S., *et al.*
Karlson, A. G. *See* Feldman, W. H., *et al.*
——, Delaude, A., Carr, D. T., Pfeutze, K. H., and Feldman, W. H. PAS resistance, 97
Karrer, J. *See* Hässig, A., *et al.*
Kergin, F., Bean, D., and Paul, W. Anoxia during surgery, 18
Kershner, R., and Adams, W. Chronic nonspecific pneumonitis, 10
Kilbourne, E., and Loge, P. Penicillin and antibody response, 24
Kirby, W. M. M. *See* Smith, J. W., *et al.*
Kirmse, T. W., and Lincoln, E. M. Streptomycin and Promizole for tuberculous meningitis, 20
Kissling, R. E. *See* Emmart, E. W., *et al.*
Klassen, K. P. Autogenous bone pegs in ribs, 5
Klopstock, R., and Milvihell, D. A. Postpneumothorax decortication, 4
Kneidel, J. H. Ductus arteriosus aneurysm, 76
Kobernick, S. D. *See* Moore, J. R., *et al.*
Koch, D. A. *See* Lampe, I., *et al.*
Koch, F. TB 1/E for tuberculous empyema, 78
Koenig, H., and Koenig, R. Ammonium pulmonary edema, 43
——, R., and Koenig, H. Ammonium pulmonary edema, 43
Koerner, T. A., Getz, H. R., and Long, E. R. Nutrition in experimental tuberculosis, 25
Kohn, J. L. *See* Wannamaker, L. W., *et al.*
——. *See* Shepard, K. S., *et al.*
Konzett, H., and Herb, C. O. Action of new bronchodilator, 102
Koo, S. N., and Woo, D. L., Pleural paragonimiasis, 55
Koontz, A. R. Tuberculous abscess, 96
Kouo, C. C., and Lieou, Y. C. BCG vaccination, 67
Kourilsky, R., Fourestier, M., le Boucher, Y., Boiteux, M., and Saint-Germain, E. de. Chronic bronchitis, 73
——, Kourilsky, S., Decroix, E., and Lifshitz, C. Bronchopulmonary infections, 74
Kourilsky, S. *See* Kourilsky, R., *et al.*
Kreis, B. *See* Bernard, E., *et al.*
Kymograph, roentgen, 6
Kymography, new uses of, 59

Lageröf, H. *See* Werko, L., *et al.*
Lame, E. L. *See* Pendergrass, E. P., *et al.*
Lampe, I., and Zatzkin, H. Pseudo-adenomatous basal-cell metastases, 93
——, Chrest, C. P., and Koch, D.A. Roentgen therapy of adenitis, 70
Landau, E., and Siddons, A. H. M. Treatment of postoperative atelectasis, 36
Landis, F. B., and Rothstein, E. Fluid versus elevated diaphragm, 87
Laryngitis, tuberculous, TB 1 for, 79
Lavage, bronchial, Diagnosis by, 99
Lativille, P. *See* Verger, P., *et al.*
Lawrence, E. A. *See* Crane, P., *et al.*
——, H. S. Tuberculin hypersensitivity transferred to man, 100
Lawson, H. M. Disseminated ossification of the lungs, 10
Lefler, J. S. *See* Weiser, R. S., *et al.*
Lehmann, J. PAS therapy in Sweden, 96
Leiner, G. C. *See* Rubin, E. H., *et al.*
Le Melletier, J., Delord, M., Heckenroth, M., and Giron, J. Tuberculous mediastinal adenopathy, 49
Lepereq, G., and Lowys, P. Round foci in childhood tuberculosis, 52

Le Prestre, C., and Melletier, J. le. Tuberculin sensitivity in primary tuberculosis, 69
Lerner, H. H. *See* Crane, P., *et al.*
Lesions, lung, Coccidioidomycotic, 8
——, ——, in rheumatoid arthritis, 11
——, osseous, of sarcoidosis, 18
—— simulating bronchiogenic carcinoma, 14
Lester, W., Jr., Robertson, O. H., Puck, T. T. and Wise, H. Bactericidal action of triethylene glycol, 67
Leukocytes, lysis of, Plasma factor for, 25
Lévi-Valensi, A., Cviklinsky, S., and Vaugier, M. Virulence of tubercle bacilli, 100
Lewis, W. G., and Tarshis, M. S. Demonstration of acid-fast bacilli in sputum, 66
Leys, D. G., and Swift, P. N. Lung lesions in rheumatoid arthritis, 11
Lieou, Y. C., and Kouo, C. C. BCG vaccination, 67
Lifshitz, C. *See* Kourilsky, R., *et al.*
Limarzi, L. R., and Paul, J. T. Sternal marrow in Hodgkin's disease, 91
Lincoln, E. M., and Kirmse, T. W. Streptomycin and Promizole for tuberculous meningitis, 20
Lindblom, K. *See* Alström, C.-H., *et al.*
Linhares, H. *See* Fontes-Magarão, M., *et al.*
Lithiasis, bronchopulmonary, active, 90
Liver biopsy, 69
—— —— in miliary tuberculosis, 50
Livingstone, R., and Morlock, H. V. Sulphetrone for pulmonary tuberculosis, 97
Lodmell, E. A., and Capps, S. C. Pneumothorax with metastatic sarcoma, 15
Loeffler's syndrome, 74
Logan, A., and Nicholson, H. Chronic suppurative pneumonia, 53
Loge, P., and Kilbourne, E. Penicillin and antibody response, 24
Logg, M. H., and Nagley, M. M. PAS for pulmonary tuberculosis, 21
Long, E. R. *See* Koerner, T. A., *et al.*
——, Joan. *See* Durant, T. M., *et al.*
Lott, L. M. *See* Farinas, P. L., *et al.*
Lotte, A. *See* Bernard, E., *et al.*
Lowys, P., and Lepercq, G. Round foci in childhood tuberculosis, 52
Lucite spheres for pulmonary collapse, 51
Lumsden, E. G. S. Pneumothorax complicating pneumoperitoneum, 50
Lundholm, R., and Kabler, P. Preservation of gastric specimens, 65
Lung abscess. *See* Abscess.
—— cancer. *See* Cancer.
Lung, Carcinoma of, 58
——, cavernous hemangioma in, 76
—— changes in hyperthermia, 43
——, Diphosgene action on, 43
——, disseminated ossification of, 10
—— function after extrapleural pneumothorax, 30
—— lesions, coccidioidomycotic, 8
Lushbaugh, C. C. *See* Tobias, J. M., *et al.*
Lymph node, tuberculous, Intratracheal rupture of, 69
Lysis, white cell, by tuberculoprotein, 25
—— of leukocytes, Plasma factor for, 25

Maher-Laughann, G. P. Collapse for bilateral tuberculosis, 4
Makomaski, Z. Swiss post-war medical summary, 28
Manganese chloride for tuberculous meningitis, 40
Mann, B. Bronchiectasis, 93
——. Prognosis in cavitary tuberculosis, 1
March, D., and Dorner, R. Primary rib tumors, 15
Marrow, sternal, in Hodgkin's disease, 91
Marshak, A., Schaeffer, W. B., and Rajagopalan, S. Usnic acid derivatives, 23
Marshall, L. A., and Specht, H. Respiratory water vapor, 43
Martin, A. R. *See* Hoggarth, E., *et al.*
——, F., and Ritvo, M. Friedländer pneumonia, 73
Martines-Botelho, G. Thoracoplasty, 30
Marty. *See* Duroux, A., *et al.*
Mason, G. A. Carcinoma of lung, 58
Matos, G. de. Feldman, J., and Oliveira-Lucena, A. de. Correlationship of the tuberculin test with other factors, 47
Mattei, C. *See* Mattei, Ch., *et al.*
——, Ch., Tristani, M., Balozet, P., and Mattei, C. Streptomycin and pneumothorax 37
Maurer, G. Cavernostomy and tamponade with PAS, 87
Maxwell, E., Ward, T., and Van Metre, T., Jr. Influenza virus in pneumonia, 9
McClellan, G. *See* Johnson, H., *et al.*
McConnell, W. J. Triethylene glycol for cold prevention, 48
McCord, C. P. Pneumoconiosis caused by graphite, 75
McCort, J. J. Chest pathology in infectious mononucleosis, 75

McDermott, W. Streptomycin for tuberculosis, 19
McDonald, J. R., Harrington, S. W., and Clagett, O. T. Origin of sputum in lung cancer, 16
——, and Woolner, L. B. Sputum cytology in bronchial carcinoma, 77
McDougall, J. B. WHO and tuberculosis, 47
Mediastinal adenopathy, tuberculous, 49
—— tumor. *See* Tumor
Medical students, tuberculosis in, 84
Medium, Dubos, with penicillin, 26
Mejer, F. Visual disturbances with streptomycin, 39
Melletier, J. le, and Le Prestre, C. Tuberculin sensitivity in primary tuberculosis, 69
Mendilaharsa, C. *See* Ferrar, M., *et al.*
Meningeal tuberculosis. *See* Tuberculosis.
Meningitis, tuberculous, Manganese chloride for, 40
——, ——, Streptomycin for, 38, 60, 79
——, ——, ——, and Promizole for, 20
Menj, M. J., and Podgaezkaja, M. G. Vitamin D_3 for skin tuberculosis, 70
Meredith, H. C., Jr. and Graddock, C. G. Liver biopsy in miliary tuberculosis, 50
Merkel, W. Agranulocytosis with thiosemicarbazone, 79
Mesothelioma, pleural, 36
Metabolism, bacterial, PAS for, 23
Metastases, pseudo-adenomatous basal-cell, 93
Metastatic sarcoma. *See* Sarcoma.
Meyer, A., Dubois de Montreynaud, J., and Sistier, J. Pulmonary segments, 49
Mice in diagnosis of tuberculosis, 65
Middlemiss, J. H. Enthema nodosum, 29
Miliary coccidioidomycosis. *See* Coccidioidomycosis.
—— tuberculosis. *See* Tuberculosis.
Miller, F. J. W. Tuberculosis in childhood, 46
——, J. B. Surface-active agents via aerosol, 39
——, J. M., Favour, C. B., Wilson, B. A., and Umbarger, M. A. Plasma factor for lysis of leukocytes, 25
——, Plasma factor in cytolysis by tuberculin, 82
——, Vaughan, J. H., and Favour, C. B. Complement in tuberculin cytolysis, 100
Millner, T., and Hurst, A. Tuberculosis and antihistaminics, 86
Milvihill, D. A., and Klopstock, R. Post-pneumothorax decortication, 4
Mindlin, J. *See* Shamaskin, A., *et al.*
Minimal tuberculosis. *See* Tuberculosis.
Mitchell, R. S. Streptomycin resistance and cavities, 59
Mitchison, D. A. Streptomycin sensitivity of tubercle bacilli, 81
Mitral disease, hemosiderosis in, 10
—— stenosis. *See* Stenosis.
Moniliasis, bronchopulmonary, Surgery for, 16
Mononucleosis, infectious, Chest pathology in, 75
Moody, J. D. Endobronchial occlusion for pulmonary resection, 17
Moore, J. A., Murphy, J. D., and Elrod, P. D. Streptomycin in pulmonary resection, 21
——, J. R., Kobernick, S. D., and Wigglesworth, F. W. Pathology of bronchiectasis, 18
Moreau. *See* Duroux, A., *et al.*
Morgenstern, P., Carr, C. E., and Nalls, W. L. Planigrams in tuberculosis, 87
Morlock, H. V., and Livingstone, R. Sulphetrone for pulmonary tuberculosis, 97
Morris, L. C. *See* Shamaskin, A., *et al.*
Morrow, A. G. *See* Scott, H. W., Jr., *et al.*
Mortality figures, unexplained, 48
——, tuberculosis, in urban Peru, 48
Much's granules, Staining of, 82
Murphy, J., and Elrod, P. Decortication of hemopneumothorax, 17
——, J. D. *See* Moore, J. A., *et al.*
Mycobacterium paratuberculosis, 66
M. tuberculosis, Antibiotics against, 97
——, Cultivation of, 26
Myerson, R. M. Spontaneous pneumothorax, 2

Nagley, M. M., and Logg, M. H. PAS for pulmonary tuberculosis, 21
Nalls, W. L. *See* Morgenstern, *et al.*
Nancekieville, L. Idiopathic hemosiderosis, 9
Nascimento, E. A. do, and Alvim, A. C. Streptomycin sensitivity, 22
Needle aspiration in lung cancer, 36
Nelson, C. R., and Corper, H. J. Concentration of acid-fast bacilli, 45
Neohetramine in experimental tuberculosis, 25
Neoplastic disease, Chemotherapy of, 98
Netherlands Seal Sale, 48
Neuhauser, E. B. D. Vascular tracheal constriction, 76
Neurogenic tumors. *See* Tumors.
Neves, A., and Ibiapina, A. Pneumoperitoneum for pulmonary tuberculosis, 31
Nicholson, D. P. Pulmonary collapse in pertussis, 11

Nicholson, H., and Logan, A. Chronic suppurative pneumonia, 53
Nocardia extracts, Tuberculostasis with, 23
Nocardiosis, 8, 33, 55
Nodes, cervical, Tuberculosis of, 49
Nonoccupational berylliosis, 54
Novak, J. Tuberculin skin tests, 103
Nutrition in experimental tuberculosis, 25

O'Brien, E. *See* Day, J., *et al.*
Obstetrical coccidioidomycosis, 55
—— tuberculosis, 29
Obstructions of respiratory tract, 58
Occlusion, endobronchial, for pulmonary resection, 17
Oliveira-Lucena, A. de. *See* Matos, G. de, *et al.*
Olsen, A., and Harrington, S. Esophageal hernias of the short esophagus type, 13
Olshaker, B. *See* Recinos, A. Jr., *et al.*
O'Neill, T. J. E. *See* Bailey, C. P., *et al.*
Opiate addiction, Infarcts in, 56
Oppenheimer, M. J. *See* Durant, T. M., *et al.*
Oosthuizen, S. F., and Fainsinger, M. H. Hydatid disease, 90
Orthoxine in bronchial asthma, 56
Osborne, R. *See* Youmans, G. P., *et al.*
Osseous lesions. *See* Lesions.
—— tuberculosis. *See* Tuberculosis.
Ossification, disseminated, of the lungs, 10
Ostrum, H. W. *See* Pendergrass, E. P., *et al.*
——, and Serber, W. Early roentgen recognition of lower-lobe tuberculosis, 6
Otis, A. B., and Rahn, H. Respiratory acclimatization to altitude, 42
Otte, H. and Pribilla, W. Anemia due to thiosemicarbazone, 79
Owens, W. I., and Holt, J. F. Osseous lesions of sarcoidosis, 18

Packalén, T., and Bergqvist, S. Hyaluronidase in tuberculosis, 100
Packer, G. L., and Weinberg, S. J. Ephedrin-penicillin inhalation, 40
Paley, P. V. *See* Bernard, E., *et al.*
Palmer, C. E. *See* Goddard, J. C., *et al.*
Pancoast-Tobias syndrome, 92
Pancreas, Cystic fibrosis of, 11
Pancreatic fibrosis. *See* Fibrosis.
Papanicolaou, B., and Papastathopoulos, Photofluorographic survey in Greece, 103
——, G. N. *See* Watson, W. L., *et al.*
Papastathopoulos and Papanicolaou, B. Photofluorographic survey in Greece, 103
Para-aminosalicyclic acid, Effect of, 22
Paraffinomas, Carcinoma from, 92
Paraguay, Hydatid disease in, 91
Paragonimiasis, pleural, 55
Parkinson, T. Eosinophilic xanthomatous granuloma, 35
PAS, aerosol, for tuberculosis, 81
—— for pulmonary tuberculosis, 21
—— tuberculosis, 21
—— in bacterial metabolism, 23
—— —— experimental tuberculosis, 62
—— resistance, 97
—— therapy in Sweden, 96
—— with cavernostomy and tamponade, 87
Patch test, Pseudoreactions to, 68
—— ——, tuberculin, 68
Pathology of bronchiectases, 18
—— —— chest in infectious mononucleosis, 75
Patnode, R. A., Cummings, M. M., and Spendlove, G. A. Mice in diagnosis of tuberculosis, 65
Patt, H. M. *See* Tobias, J. M., *et al.*
Patterson, P. R. *See* Schwachman, H., *et al.*
Paul, J. T., and Limarzi, L. R. Sternal marrow in Hodgkin's disease, 91
—— W. *See* Kergin, F., *et al.*
Paulson, D., and Shaw, R. Resection for lung abscess, 16
Paulino, F. Thoracoplasty, 30
Payne, T. P. B. *See* Scott, H. W., Jr., *et al.*
Pelnáru, P. Pulmonary function, 67
Pendergrass, E. P., Lame, E. L., and Ostrum, H. W. Hemosiderosis in mitral disease, 10
Penicillin and antibody response, 24
—— atomization, Intratracheal, 81
——, Dubos medium with, 26
—— -ephedrin inhalation, 40
Pentti, M. Tuberculosis of cervical nodes and tonsils, 49
Perianes, I., and Cossio, P. Surgical treatment of "cardiac lung", 57
Peristalsis, bronchial, 77
Perry, T. L. Aureomycin in treatment of experimental tuberculosis, 98
Pertussis, pulmonary collapse in, 11
Peru, urban, Tuberculosis mortality in, 48
Petersen, A. B. *See* Richardson, H. L., *et al.*
Pfeutze, K. H. *See* Karlson, A. G., *et al.*
Phagocytic activity of bone marrow, 82
Photofluorographic survey in Greece, 103
Phrenicectomy, endoscopic, 31
Phrenic vessels, Aneurysm of, 94
Pietrowski, J. J., and Graessle, O. E. Effect of para-aminosalicyclic acid, 22

Piotet, G. Cutaneous primary complex, 1
Pittman, H. S., and Schatzki, R. Conflagration pneumonitis, 92
Planigrams in tuberculosis, 87
Plasma factor for lysis of leukocytes, 25
—— —— in cytolysis by tuberculin, 82
Pleural cavity. *See* Cavity.
—— mesothelioma, 36
—— paragonimiasis, 55
—— pneumonectomy, 50
Pneumoconiosis caused by graphite, 75
—— in graphite workers, 75
Pneumonectomy, 5
——, pleural, 50
Pneumonia, atypical, Aureomycin for, 98
——, chronic suppurative, 53
——, eosinophilic, 52
——, Friedländer, 73
——, ——, acute, 88
—— in children, Chloromycetin for, 81
——, Influenza virus in, 9
——, Q fever, 88
——, chronic cholesterol, 88
Pneumonitis, chronic nonspecific, 10
——, conflagration, 92
Pneumonolysis, extrapleural, 4
——, intrapleural, 3
Pneumoperitoneum, 69
—— and strangulated hernia, 31
—— for pulmonary tuberculosis, 31
——, Pneumothorax complicating, 50
Pneumothorax and blood elements, 83
—— —— streptomycin, 37
—— complicating pneumoperitoneum, 50
——, extrapleural, 3
——, ——, Lung function after, 30
—— in elderly subjects, 31
——, spontaneous, 2, 94
—— with metastatic sarcoma, 15
Podgaezkaja, M. G., and Menj, M. J. Vitamin D_2 for skin tuberculosis, 70
Podlaha, J. Thoracoplasty, 86
Pope, H. Growth inhibition of tubercle bacilli, 64
Poppel, M. H. *See* Grishman, A., *et al.*
Postel, S. *See* Tobias, J. M., *et al.*
Postoperative atelectasis. *See* Atelectasis.
Postpneumothorax decortication, 4
Post-war, Swiss, medical summary, 28
Potts, W. Potts operation for pulmonary stenosis, 17
Pregnancy in pulmonary tuberculosis, 1
Pressure, intracranial, Pulmonary effects of, 44
——, vascular pulmonary, 45
Pribilla, W., and Otte, H. Anemia due to thiosemicarbazone, 79
Promizole and streptomycin for tuberculous meningtis, 20
Pseudo-adenomatous metastases. *See* Metastases.
Pseudotuberculosis, human, 54
Puck, T. T. *See* Lester, W., Jr., *et al.*
Pugsley, H. E., and Spence, P. McK. Pancreatic cystic fibrosis, 11
Pulmonary abscess. *See* Abscess.
—— absorption, 62
—— adenomatosis, 35, 76
—— arterio-sclerosis, 33
—— artery, anomalous, 93
—— aspergillosis, 55
—— calcifications. *See* Calcifications.
—— brucellosis. *See* Brucellosis.
—— coccidioidomycosis. *See* Coccidioidomycosis.
—— collapse. *See* Collapse.
—— cysts, 14
—— disease, Epidemic of, 7
—— edema. *See* Edema.
—— embolism, 34
—— effects of intracranial pressure, 44
—— fibrosis, 34
—— function, 67
—— resection. *See* Resection.
—— schistosomiasis, 73
—— segments, 49
—— stenosis. *See* Stenosis.
—— tuberculosis. *See* Tuberculosis.
—— vascular pressures, 45
—— xanthoma, 15
Puncture, tracheal, Emphysema in, 56
Pusterla, F. *See* Hässig, A., *et al.*
Putrid empyema, 63
Pyelitis, caseating, 3

Q fever pneumonia, 88

Rabbit, Air-borne tuberculosis in, 65
—— eye test, 22
Raffel, S., and Arnes, W. H. Tuberculo-complement-fixation in sarcoidosis, 72
Rahn, H. Alveolar air, 41
——, and Otis, A. B. Respiratory acclimatization to altitude, 42
Rajagopalan, S. *See* Marshak, A., *et al.*
Rakower, J., and Wayl, P. Tuberculosis in Yemenite Jews, 102
Reaction, serologic, in tuberculosis, 45

Reaction, skin, to tuberculin, 47
Recinos, A., Jr., Ross, S., Olshaker, B., and Trimble, E. Chloromycetin for pneumonia in children, 81
Rees, R. J. W. *See* Gardner, P. A., *et al.*
Reid, L., and Hayward, J. Cavernous pulmonary telangiectasis, 94
Renshaw, B., and Rosenbaum, H. Respiratory pathways, 44
Resection for lung abscess, 16
—— —— pulmonary tuberculosis, 4
—— —— tuberculosis, 5
——, pulmonary, Endobronchial occlusion for, 17
——, ——, Streptomycin in, 21
——, Streptomycin in, 21
Resistance of PAS, 97
Respiration and circulation, 44
——, artificial, Effect of, on circulation, 27
——, electrophrenic, 11
——, Vaccine effects on, 43
Respiratory acclimatization to altitude, 42
—— pathways, 44
—— tract obstructions, 58
—— water vapor, 43
Revuelta, R. *See* Farinas, P. L., *et al.*
Rey, J. C. *See* Vaccarezza, R. F., *et al.*
Riboflavin and growth of tubercle bacilli, 26
Rib tumors, primary, 15
Richardson, H. L., Hunter, W. C., Conklin, W. S., and Petersen, A. B. Cytohistology of bronchial secretions, 41
Ricker, W., and Clark, M. Sarcoidosis, 71
Ritvo, M., and Martin, F. Friedländer pneumonia, 73
Rivoire, R., and Colleau A. Streptomycin for tuberculous meningitis, 60
Robbins, L. L., and Sniffen, R. C. Chronic cholesterol pneumonitis, 88
Robertson, O. H. *See* Lester W., Jr., *et al.*
Robson, J. M. *See* Gardner, P. A., *et al.*
Roemmich, W. Tuberculosis after negative microfilm, 83
Roentgen kymograph, 6
—— therapy of adenitis, 70
Roost-Pauli, H., and Roost-Pauli, M. Fate of streptomycin in the colon, 96
——, M., and Roost-Pauli, H. Fate of streptomycin in the colon, 96
Rosemberg, J. Minimal tuberculosis in adults, 46
Rosenbaum, H., and Renshaw, B. Respiratory pathways, 44
Rosenberg, L. S. *See* Felson, B., *et al.*
Rosenthal, N. *See* Spitzer, J. M., *et al.*
Ross, S. *See* Recinos, A., Jr., *et al.*
Rossel, G., and Berthet, J. G. Fluid motion in hydropneumothorax, 6
Rothstein, E., and Landis, F. B. Fluid versus elevated diaphragm, 87
Rottenberg, L. A., and Golden, R. Spontaneous pneumothorax, 94
Rubin, E. H., Steinbach, M. M., Leiner, G. C., Adelsberger, L., and Zimmerman, H. M. Crystalline streptomycin, 37
Ruke, J. S., and Cazier, P. D. Histoplasmosis, 7
Rupture, intratracheal, of tuberculous lymph node, 69

Saenz, A., and Canetti, G. Willis phenomenon and streptomycin, 60
Saint-Germain, E. de. *See* Kourilsky, R., *et al.*
St. Vincent, L. *See* Weiser, R. S., *et al.*
Salvi, A. E. K. Aerosol PAS for tuberculosis, 81
Samson, P. S., and Dugan, D. J. Traumatic diaphragmatic hernia, 13
Sanger, P. W. Exploratory thoracotomy in empyema, 17
Sante, L. R. Carcinoma from paraffinomas, 92
Sarcoidosis, 71
——, Electrocardiograms in, 92
——, Osseous lesions of, 18
——, tuberculo-complement-fixation in, 72
Sarcoma, metastatic, Pneumothorax with, 15
Sarnoff, S. *See* Whittenberger, J., *et al.*
Sarroste, J., Ciosi-Frenay, and Blind, P. Surgery in bone and joint tuberculosis, 52
Schaeffer, W. B. *See* Marshak, A., *et al.*
Schatzki, R., and Pittman, S. Conflagration pneumonitis, 92
Schistosomiasis, pulmonary, 73
Schizophrenia and tuberculosis, 2
Schmidt, C. H. Tuberculosis in medical students, 84
Scholtze, H., and Viets, W. TB 1 and TB 4 for tuberculosis, 78
Schomer, A. *See* Bass, H. E., *et al.*
Schröcksnadel, H. Respiration and circulation, 44
Schultz, J., and Weiss, C. Amidase of tuberculous tissue, 100
Schwachman, H., Crocker, A. C., Foley, G. E., and Patterson, P. R. Aureomycin for pulmonary changes in pancreatic fibrosis, 24
Schwarting, V. M. *See* Feldman, W. H., *et al.*
Schwartzman, J., and Cerone, M. Tuberculin patch tests, 68
Scott, G. *See* Toplin, G. V., *et al.*

Scott, G., H. W., Jr., Morrow, A. G., and Payne, T. P. B. Pulmonary xanthoma, 15
Screening, small-film, in major cities, 83
Scudi, J. V., and Duca, C. J. Neohetramine in experimental tuberculosis, 25
Seal Sale, Netherlands, 48
Secretions, bronchial, Cytohistology of, 41
——, ——, Tumor cells in, 40
Segal, M. S. *See* Gaensler, E. A., *et al.*
Segments, pulmonary, 49
Sellors, T. H., and Hickey, M. D. Resection for pulmonary tuberculosis, 4
Sensitivity, Streptomycin, of tubercle bacilli, 81
—— to streptomycin, 22
——, tuberculin, in primary tuberculosis, 69
Serologic reaction in tuberculosis, 45
Shamaskin, A., Des Autels, E. J., Sweany, H. C., Morris, L. C., Zvetna, J. R., and Mindlin, J. Miliary and meningeal tuberculosis, 95
Shapiro, S. *See* Spitzer, J. M., *et al.*
——, V. J., and Zeigelnik, A. J. Pneumoperitoneum, 69
Shaw, J. B., and Wynn-Williams, N. Tuberculosis contact survey, 103
——, R., and Paulson, D. Resection for lung abscess, 16
Sheehan, H. L., and Whitwell, F. Staining of tubercle bacilli, 82
Shepard, K. S., Kohn, J. L., Kaplan, S. R., and Allen, T. C. Streptomycin for whooping cough, 62
Sherry, S., and Tillett, W. Enzyme treatment of empyema, 12
Shimkin, M. B., and Bierman, H. R. Chemotherapy of neoplastic disease, 98
Shires, G. T., and Holman, J. Carbon dioxide inhalation in emphysema, 41
Shunt for mitral stenosis, 57
Sicca, G. T. Phagocytic activity of bone marrow, 82
Siddons, A. H. M., and Landau, E. Treatment of postoperative atelectasis, 36
Sigurdsson, B., and Tryggvadotter, A. G. *Mycobacterium paratuberculosis*, 66
Sikl, H. Anomalous pulmonary artery, 93
Silicosis, Egg shell calcifications in, 89
Silverman, I. and Friedman, E. BCG tuberculin test, 103.
Simpson, R. S. *See* Grishman, A., *et al.*
Sinuses, tuberculous, Streptomycin for, 80
Sistier, J. *See* Meyer, A., *et al.*
Skin reaction to tuberculin, 47
Skin tuberculosis. *See* Tuberculosis
Smale, L. E., and Birsner, J. W. Obstetrical coccidioidomycosis, 55
Small-film screening in major cities, 83
Smears, bronchial in cancer, 16
Smith, D. T. Medical treatment of pulmonary abscesses, 12
——, J. W., Humiston, J., Cregar, W. P., and Kirby, W. M. M. Dubos medium with penicillin, 26
Sniffen, R. C., and Robbins, L. L. Chronic cholesterol pneumonitis, 88
Solomidès, J., and Boulaud, E. PAS in experimental tuberculosis, 62
Sommer, E. Tomography of tuberculous spondylitis, 7
Soubrie, A. *See* Vaccarezza, R. F., *et al.*
Specht, H., and Marshall, L. A. Respiratory water vapor, 43
Specimens, gastric, Preservation of, 65
Spence, P. McK., and Pugsley, H. E. Pancreatic cystic fibrosis, 11
Spendlove, G. A. *See* Patnode R. A. *et al.*
Spinks, A. Blood concentration of thiosemicarbazones, 39
Spitzer J. M., Rosenthal, N., Weiner, M., and Shapiro, S. Pulmonary embolism, 34
Splenomegaly, tuberculous, 2
Spondylarthritis, 37
Spondylitis, tuberculous, Tomography of, 7
Sprigg, J. B. *See* Gledhill, E. Y., *et al.*
Sputum cytology in bronchial carcinoma, 77
——, Demonstration of acid-fast bacilli in, 66
——, Origin of, in lung cancer, 16
Staines, E. Diagnosis by bronchial lavage, 99
Stark, T. H. *See* Emmart, E. W., *et al.*
Stauffer, M., and Jorgens, J. Electrokymography, 18
Steadman, L. T. *See* Eisenbud, M., *et al.*
Steele, J. *See* Unger, P., *et al.*
Steenken, W. Jr., and Wolinsky, E. Tuberculostatic effect of subtilin, 23
Steinbach, M. M. *See* Rubin, E. H., *et al.*
Steinberg, I., and Dotter, C. T. Angiocardiography, 19
Differentiation of mediastinal tumor and aneurysm, 77
Stenosis, mitral, Shunt for, 57
——, pulmonary, Operation for, 17
——, ——, Valvulotomy for, 57
Storey, N. E. *See* Hoggarth, E., *et al.*
Streptomycin and hydrocephalus, 38
—— —— pneumothorax, 37

Streptomycin and Promizole for tuberculous meningitis, 20
—— —— Willis phenomenon, 60
——, crystalline, 37
—— dependent tubercle bacilli, 61
——, Fate of, 95
——, —— ——, in the colon, 96
—— for childhood tuberculosis, 38
—— —— pulmonary tuberculosis, 80
—— —— tuberculosis, 19
—— —— tuberculous meningitis, 38, 60, 79
—— —— —— sinuses, 80
—— —— whooping cough, 61, 62
—— in pulmonary resection, 21
—— —— pleural cavity 22
—— resistance and cavities, 59
—— resistant tubercle bacilli, Transmission of, 61
—— sensitivity, 22
—— —— of tubercle bacilli, 81
—— therapy, 59
——, Toxicity of, 38
——, Visual disturbances with, 39
Stutz, E. TB 1 for tuberculous laryngitis, 79
Subtilin, Tuberculostatic effect of, 23
Sude, G. Miliary tuberculosis, 69
Sullivan, H. Extrapleural pneumothorax, 3
Sulphetrone for pulmonary tuberculosis, 97
Suppurative pneumonia. *See* Pneumonia.
Surface-active agents. *See* Agents.
Surgery, Anoxia during, 18
—— in bone and joint tuberculosis, 52
Survey, photofluorographic, in Greece, 103
——, Tuberculosis contact, 103
Sussman, M. L. *See* Grishman, A., *et al.*
Sweany, H. C. *See* Shamaskin, A., *et al.*
Sweden, PAS therapy in, 96
Sweet, R. H. Intrathoracic goiter, 14
——, and Bland, E. F. Shunt for mitral stenosis, 57
Swift, M. N. *See* Tobias, J. M., *et al.*
——, P. N., and Leys, D. G. Lung lesions in rheumatoid arthritis, 11
Swiss post-war medical summary, 28
Sympathectomy for asthma, 13
Syndrome, Loeffler's, 74
——, Pancoast-Tobias, 92

Tamponade and cavernostomy with PAS, 87
Tarshis, M. S., and Lewis, W. G. Demonstration of acid-fast bacilli in sputum, 66
TB 1 and TB 4 for tuberculosis, 78
—— for tuberculous laryngitis, 79
TB 1/E for tuberculous empyema, 78
TB 4 and TB 1 for tuberculosis, 78
Teixeira, J. Tuberculous empyema, 30
Telangiectasis, cavernous pulmonary, 94
Test, BCG tuberculin, 103
——, Congo Red, 27
——, Rabbit eye, 22
——, tuberculin, Correlationship with other factors, 47
——, Tuberculin skin, 103
Thiosemicarbazone, Agranulocytosis with, 79
——, Anemia due to, 79
——, Blood concentrations of, 39
—— for tuberculosis, 39
Thompson, S. Effect of artificial respiration on circulation, 27
Thoracoplasty, 30, 86
——, rib fracture after, 6
Thoracotomy, exploratory, in empyema, 17
Tidy, H. Pulmonary arterio-sclerosis, 33
Tillett, W., and Sherry, S. Enzyme treatment of empyema, 12
Tissue, tuberculous, Amidase of, 100
Tobias, J. M., Postel, S., Patt, H. M., Lushbaugh, C. C., Swift, M. N., and Gerard R. W. Diphosgene action on lung, 43
Tobie, W. C., and Jones, M. J. PAS in bacterial metabolism, 23
Todd, R. McL. Streptomycin for childhood tuberculosis, 38
Tomography in tuberculosis, 84
——, New types of, 32
—— of tuberculous spondylitis, 7
Tonsils, Tuberculosis of, 49
Taplin, G. V., Gropper, A. L., Scott, G., and Hageman, J. R. Micronized aminophylline for asthma, 12
Toxicity of streptomycin, 38
Tracheal constriction, vascular, 76
—— puncture. *See* Puncture.
Triethylene glycol for cold prevention, 48
Trimble, E. *See* Recinos, A., Jr., *et al.*
Tristani, M. *See* Mattei, Ch., *et al.*
Trithylene glycol, Bactericidal action of, 67
Tryggvadotter, A. G., and Sigurdsson, B. *Mycobacterium paratuberculosis*, 66
Tubercle bacilli. *See* Bacilli
Tuberculin cytolysis, Complement in, 100
—— sensitivity. *See* Sensitivity
—— patch tests, 68
——, Plasma factor in cytolysis by, 82
——, Skin reaction to, 47
—— —— tests, 103
—— test, Correlationship with other factors, 47

Tuberculo-complement-fixation in sarcoidosis, 72
Tuberculocidal compounds, new, 98
Tuberculoprotein, White cell lysis by, 25
Tuberculosis, Aerosol PAS for, 81
—— after negative microfilm, 83
——, air-borne, in the rabbit, 65
—— and antihistaminics, 86
—— —— schizophrenia, 2
—— —— WHO, 47
——, Antihistaminic drugs for, 3
——, avian, 71
——, ——, in a child, 85
——, bilateral, Collapse for, 4
——, bone and joint, Surgery in, 52
——, cavitary, 1
——, childhood, Round foci in, 52
—— contact survey, 103
——, experimental, Aureomycin in treatment of, 98
——, ——, Neohetramine in, 25
——, ——, Nutrition in, 25
——, ——, PAS in, 62
——, Hyaluronidase in, 100
—— in Bolivia, 27
—— —— childhood, 46
—— —— children, Streptomycin for, 38
—— —— England and Wales, 48
—— —— medical students, 84
—— —— Yemenite Jews, 102
——, lower lobe, 1, 6
——, Mice in diagnosis of, 65
——, miliary, 69
——, ——, Liver biopsy in, 50
——, —— and meningeal, 95
—— minimal, in adults, 46
—— mortality in urban Peru, 48
——, obstetrical, 29
—— of skin, Vitamin D_2 for, 70
——, osseous, of the hand, 31
——, PAS for, 21
——, Planigrams in, 87
——, primary, 85
——, ——, Tuberculin sensitivity in, 69
——, pulmonary, Dihydrostreptomycin for, 19
——, ——, Pneumoperitoneum for, 31
——, ——, Pregnancy in, 1
——, ——, Resection for, 4
——, ——, Streptomycin for, 80
——, ——, Sulphetrone for, 97
——, Resection for, 5
——, Serologic reaction in, 45
——, Streptomycin for, 19
——, TB 1 and TB 4 for, 78
Tuberculosis, Thiosemicarbazones for, 39
——, Tomography in, 84
Tuberculostasis with Nocardia extracts, 23
Tuberculostatic action of chloromycetin, 23
—— effect of subtilin, 23
Tuberculous abscess, 96
—— empyema, 29, 30
—— lymph node. *See* Lymph nodes
—— mediastinal adenopathy, 49
—— meningitis. *See* Meningitis.
—— tissue. *See* Tissue.
Tucker, F. C., and Hirsch, E. F. Nocardiosis, 8, 55
Tumor cells in bronchial secretions, 40
——, mediastinal, Differentiation of, and aneurysm, 77
——, intrathoracic, neurogenic, 36
——, solitary, of chest, 15
——, rib, 15
Turner, W. M. L., and Angelman, H. Intratracheal rupture of tuberculous lymph node, 69

Uehlinger, E., and Gloor, H. U. Caseating pyelitis, 3
Umbarger, M. A. *See* Miller, J. M., *et al.*
Unger, P., Zuckerbrod, M., Beck, G., and Steele, J. New Congo Red test, 27
Usnic acid derivatives, 23

Vaccarezza, R. F., Soubrie, A., and Rey, J. C. Lung function after extrapleural pneumothorax, 30
Vaccination, B.C.G., 67
—— ——, Apparatus for, 47
——, ——, in Brazil, 46, 84
Vaccine effects on respiration, 43
Valvulotomy for pulmonary stenosis, 57
Vanderlinde, R. J. *See* Yegian, D., *et al.*
Van Dienst, Mej. G. C. Jos. Netherlands Seal Sale, 48
Van Metre, T., Jr. *See* Maxwell, E., *et al.*
Van Ordstrand, H. S. *See* DeNardi, J. M., *et al.*
Vapor, water, respiratory, 43
Vargas-Sivila, E. Tuberculosis in Bolivia, 27
Variant of avian bacillus, 45
Vascular pressures, 45
—— tracheal constriction, 76
Vaughan, J. H., *See* Miller, J. M., *et al.*
Vaugier, M. *See* Lévi-Valensi, A., *et al.*
Ventilation, collateral intralobar, 26
Vergani, F. Incoagulability of intrapleural blood, 83

Verger, P., Bentegeat, J., and Lativille, P. Pneumothorax complicating pneumoperitoneum, 50
Verges. *See* Duroux, A., *et al.*
Vessels, intrapulmonary, in congenital heart disease, 34
Vidal, C. *See* Carvalho, L. de, *et al.*
Vieira, A. *See* Fontes-Magarão, M., *et al.*
Viets, W, and Sholtze, H. TB 1 and TB 4 for tuberculosis,78
Vineberg, A. M. Healing of tuberculous pulmonary cavities, 86
Virulence of tubercle bacilli, 100
Visscher, M. B. *See* Campbell, G. S., *et al.*
——. *See* Haddy, F. J., *et al.*
Vitagliano, G. R. *See* Allison, S. T., *et al.*
Vitamin D_3 for skin tuberculosis, 70
Volk, R. *See* Allison, S. T., *et al.*
Vollmer, H. Pseudoreactions to the patch test, 68

Wales, Tuberculosis in, 48
Walker, W. J. Acute pulmonary abscess, 35
Wallertshauser, M. Eosinophilic pneumonia, 52
Wallgren, A., and Wegelius C. Primary tuberculosis, 85
Wannamaker, L. W., Kohn, J. L., and Weichsel, M. Streptomycin for whooping cough, 61
Wanta, R. C. *See* Eisenbud, M., *et al.*
Ward, T. *See* Maxwell, E., *et al.*
Watson, W. L., Cromwell, H., Craver, L., and Papanicolau, G. N. Bronchial smears in cancer, 16
Wayl, P., and Rakower, J. Tuberculosis in Yemenite Jews, 102
Webster, M. R. *See* Durant, T. M., *et al.*
Wegelius, C., and Wallgren, A. Primary tuberculosis, 85
Weichsel, M. *See* Wannamaker, L. W., *et al.*
Weinberg, S. J., and Packer, G. L. Ephedrin-penicillin inhalation, 40
Weiner, M. *See* Spitzer, J. M., *et al.*
Weiser, R. S., Gardner, G. M., Lefler, J. S., and St. Vincent, L. Antibiotics against *M. tuberculosis*, 97
Weiss, C., and Schultz, J. Amidase of tuberculous tissue, 100
Wells, E. B. *See* Collins, H. S., *et al.*
Werko, L., Berseus, S., and Lageröf, H. Cardiac output studies, 27
Whittenberger, J., Sarnoff, S., and Hardenbergh, E. Electrophrenic respiration, 11
Whitwell, F., and Sheehan, H. L. Staining of tubercle bacilli, 82
WHO and tuberculosis, 47
Whooping cough, Streptomycin for, 61, 62
Wichelhausen, R. H., and Brennan, A. J. Transmission of streptomycin-resistant tubercle bacilli, 61
Wigglesworth, F. W. *See* Moore, J. R., *et al.*
Willis phenomenon and streptomycin, 60
Wilson, B. A. *See* Miller, J. M., *et al.*
Wise, H. *See* Lester, W., Jr., *et al.*
Wolf, B. S. *See* Eisenbud, M., *et al.*
Wolinsky, E., and Steenken, W. Jr. Tuberculostatic effect of subtilin, 23
Woo, D. L., and Koo, S. N. Pleural paragonimiasis, 55
Woolner, L. B., and McDonald, J. R. Sputum cytology in bronchial carcinoma, 77
Wynn-Williams, N. Pneumoperitoneum and strangulated hernia, 31
——. Tomography in tuberculosis, 84
——, and Shaw, J. B. Tuberculosis contact survey, 103

Xanthoma, pulmonary, 15
Xanthomatous granuloma. *See* Granuloma.

Yater, W. M., Finnegan, J., and Giffin, H. M. Arteriovenous fistula, 94
Yegian, D., Budd, V., and Vanderlinde, R. J. Streptomycin-dependent tubercle bacilli, 61
Yesner, R., and Hurwitz, A. Surgery for broncho-pulmonary moniliasis, 16
Youmans, A. S., and Youmans, G. P. Rate of growth of tubercle bacilli, 64
——. *See* Youmans, G. P., *et al.*
——, G. P., and Youmans, A. S. Rate of growth of tubercle bacilli, 64
——, Youmans, A. S., and Osborne, R. Tuberculostatic action of chloromycetin, 23
Young, E. H. P. *See* Hoggarth, E., *et al.*
——, R. M. *See* Hager, H. F., *et al.*

Zatzkin, H., and Lampe, I. Pseudo-adenomatous basal-cell metastases, 93
Zcigelnik, A. J., and Shapiro, V. J. Pneumoperitoneum, 69
Zimmerman, H. M. *See* Rubin, E. H., *et al.*
Zuckerbrod, M. *See* Unger, P., *et al.*
Zvetna, J. R. *See* Shamaskin, A., *et al.*

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF THE AMERICAN TRUDEAU SOCIETY
Medical Section of National Tuberculosis Association

ABSTRACTS

EDITOR-IN-CHIEF
ESMOND R. LONG
Philadelphia, Pa.

MANAGING EDITOR
WALSH MCDERMOTT
New York, N. Y.

EDITORIAL BOARD

W. EDWARD CHAMBERLAIN, Philadelphia, Pa.
HALBERT L. DUNN, Washington, D. C.
H. CORWIN HINSHAW, San Francisco, Calif.
KIRBY S. HOWLETT, JR., Shelton, Conn.
JOHN C. JONES, Los Angeles, Calif.
ALEXANDER D. LANGMUIR, Baltimore, Md.
HERBERT C. MAIER, New York, N. Y.
WILLIAM P. SHEPARD, San Francisco, Calif.
C. EUGENE WOODRUFF, Northville, Mich.

VOLUME 61

JANUARY-JUNE, 1950

PUBLISHED MONTHLY

AT MOUNT ROYAL AND GUILFORD AVENUES, BALTIMORE 2, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JANUARY, 1950

Chemical Studies on Thiosemicarbazones with Particular Reference to Antituberculous Acitivity. ROBERT BEHNISCH, FRITZ MIETZSCH, AND HANS SCHMIDT 1

Investigations on the Antituberculous Activity of the Thiosemicarbazones *In Vitro* and *In Vivo*. GERHARD DOMAGK 8

The Present Status of the Chemotherapy of Tuberculosis with Conteben, a Substance of the Thiosemicarbazone Series. A Review. ANTON MERTENS AND ROLF BUNGE 20

The Implications of Changing Morbidity and Mortality Rates from Tuberculosis. HERBERT R. EDWARDS AND G. J. DROLET 39

Prevalence of Clinically Significant Pulmonary Tuberculosis among Inmates of New York State Penal Institutions. JULIUS KATZ AND ROBERT E. PLUNKETT 51

Postoperative Management of Thoracoplasty Patients. JOHN ALEXANDER 57

The Value of Cytological Diagnosis of Pulmonary Malignancy. LOUIS H. CLERF AND PETER A. HERBUT 60

Properties of a Culture of BCG Grown in Liquid Media Containing Tween 80 and the Filtrate of Heated Serum. RENE J. DUBOS, FRANK FENNER, AND CYNTHIA PIERCE 66

Experimental Pulmonary Tuberculosis in the Dog. Comparison of Lesions in Puppies and in Mature Dogs. FRANCIS D. GUNN AND JOHN J. SHEEHY 77

Studies on the Contagiousness of Coccidioidomycosis. II. The Fate of Spherules in Sputum Exposed Out of Doors. SOL ROY ROSENTHAL AND FRANCIS H. ELMORE 95

Studies on the Contagiousness of Coccidioidomycosis. III. Infection in Guinea Pigs by Contact with Diseased Animals. SOL ROY ROSENTHAL AND FRANCIS H. ELMORE 106

Tuberculosis of the Stomach and the Stomach in Tuberculosis: A Review with Particular Reference to Gross Pathology and Gastroscopic Diagnosis. EDDY D. PALMER 116

Case Reports:

Pulmonary Alveolar Adenomatosis. JOHN H. MOYER 131

Miliary Tuberculosis: Report of a Case of Long Duration without Chemotherapy. HARRY R. MCPHEE 138

American Trudeau Society: Report to Clinical Subcommittee on German Experience with Thiosemicarbazone. H. CORWIN HINSHAW AND WALSH MCDERMOTT 145

Letters to the Editors:

Pulmonary Coccidioidomycosis. H. E. BASS 158

Abstracts 1

NUMBER 2, FEBRUARY, 1950

Streptomycin-Promizole Therapy of Miliary and Meningeal Tuberculosis in Children. EDITH M. LINCOLN AND THOMAS W. KIRMSE 159
The Effect of Streptomycin upon the Pathology of Tuberculous Meningitis. WILLIAM J. WINTER 171
Tuberculous Bronchitis in Pulmonary Resection. MAURICE G. BUCKLES AND WILFORD B. NEPTUNE 185
The Use of Gelatin Foam (Gelfoam) in Thoracoplasties. GUSTAF A. HEDBERG, WILLIAM D. SEYBOLD, AND O. THERON CLAGETT 193
Studies on the Respiratory Gas Exchange in One Hundred Anthracite Coal Miners with Pulmonary Complaints. HURLEY L. MOTLEY, LEONARD P. LANG, AND BURGESS GORDON 201
Para-aminosalicylic Acid Treatment of Tuberculosis. A Review. EMIL BOGEN 226
Case Reports:
Thrombosis of Cerebral Vessels with Necrosis of the Basal Nuclei. R. H. RIGDON AND EDWARD J. LEFEBER 247
A Case of Generalized Hemangio-Sarcomatosis Erroneously Considered as Generalized Tuberculosis. MARTHA D. COLLINS AND HYMAN FISHER 257
Editorial: Specific Therapy for Tuberculous Meningitis. PAUL A. BUNN 263
Letters to the Editors:
Sensitivity to Histoplasmin. RUBY G. KELLY AND C. EUGENE WOODRUFF 269
Enzymatic Characteristics of Suspensions of Different Mycobacteria. HUBERT BLOCH 270
Books 272
American Trudeau Society: Report of the Laboratory Subcommittee of the Committee on Medical Research and Therapy, and of the Subcommittee on Evaluation of Laboratory Procedures of the Committee on Revision of Diagnostic Standards 274
Abstracts 29

NUMBER 3, MARCH, 1950

Sarcoidosis: A Clinical and Roentgenological Study of Twenty-eight Cases. JOHN H. MOYER AND ALFRED J. ACKERMAN 299
Pneumoperitoneum with Phrenic Paralysis for Pulmonary Tuberculosis. WILLIAM J. HABEEB AND HOWARD G. REISER 323
The Electrocardiogram in Pneumoperitoneum: Including Augmented Unipolar Limb Leads and Unipolar Chest and Esophageal Leads. ELWYN EVANS AND THOMAS C. BLACK 335
The Effect of Penicillin on Wound Infection and Other Complications after Thoracoplasty. WILLIAM E. BLOOMER AND JAMES W. MAJOR 346
Appendicitis during Pneumoperitoneum Treatment. BURNETT SCHAFF AND SIEGBERT BORNSTEIN 353

Bronchoscopy in a Sanatorium: A Review of 522 Consecutive Bronchoscopies. D. M. MacRae, R. E. Hiltz, and J. J. Quinlan 355
Bronchogenic Carcinoma and Pulmonary Tuberculosis. Lawrence M. Shefts and William Hentel 369
Relationships between Tuberculosis and Bronchiectasis: A Study of Clinical and Post-mortem Material. Edna M. Jones, W. M. Peck, C. E. Woodruff, and H. S. Willis 387
The Dissemination of Tubercle Bacilli in Experimental Tuberculosis in the Guinea Pig. M. A. Soltys and A. R. Jennings 399
Studies in Tuberculosis Chemotherapy: I. Simple Primary Aromatic Amines, *in Vitro* and *in Vivo*. Leonard Doub and Guy P. Youmans. 407
Case Reports
Fatal Asphyxia as a Complication of Lucite Plombage. Erving F. Geever and William F. Stone, Jr. 422
Pneumonectomy for Pulmonary Hemorrhage in Tuberculosis. Thomas C. Ryan and William T. Lineberry, Jr. 426
Tuberculoma of the Lung, Simulating Bronchogenic Carcinoma. Isidor Kross 431
American Trudeau Society: Report of Clinical Subcommittee of the Committee on Medical Research and Therapy 436
Letters to the Editors:
Contagiousness of Coccidioidomycosis. Rudolph Berke 441
The Effect of Antihistamine Medication on the Tuberculin Reaction. Eli Friedman and Irving Silverman 442
Abstracts 49

Number 4, April, 1950

The Role of Dual Reading in Mass Radiography. J. Yerushalmy, J. T. Harkness, J. H. Cope, and B. R. Kennedy 443
Friedländer's Pneumonia. Robert H. Wylie and Paul A. Kirschner 465
Acute Lung Abscess. Wilson Weisel, Forrester Raine, and George C. Owen 474
The Resistance of Tubercle Bacilli to Chemotherapeutic Agents. Diran Yegian and Robert J. Vanderlinde 483
Experimental Studies on the Pathogenesis and Prognosis of Renal Tuberculosis. Andrew Sporer and Monroe E. Greenberger 508
The Streptomycin Treatment of Genitourinary Tuberculosis. John K. Lattimer, J. Burns Amberson, and Stanley Braham 518
The Effect of Streptomycin on the Morphology of the Tuberculous Lesion. M. Clarke Silverthorne and Gertrude Silverman 525
Pathology of Pulmonary Tuberculosis: As Modified by Streptomycin Therapy. Hugh W. Mahon 543

Effect of Intravenous Tuberculin Injection on Subsequent Tuberculin Skin Reactions in Hypersensitive Rabbits. CURTIS SANDAGE AND JORGEN M. BIRKELAND 556
The Distribution of Iron in Tuberculous Granulation Tissue. GEORGE GOMORI 560
Methods for Isolating Tubercle Bacilli. E. GWYN ROBERTS, JACK L. WALLACE, AND HENRY ERLICH 563
A Direct Method for the Determination of the Sensitivity of Tubercle Bacilli to Streptomycin. GUY P. YOUMANS, ABDULLA IBRAHIM, JOAN SWEANY, AND HENRY C. SWEANY 569
Plate Method for the Determination of Streptomycin Sensitivities of *Mycobacterium Tuberculosis*. BERKELEY H. JOHNSON 578
A Comparison between an Aneroid Spirometer and a Water Spirometer. DAVID H. COHEN 582
Editorial: Tuberculosis on the Navaho Reservation. LEWIS J. MOORMAN ... 586
Books 592
Abstracts 69

NUMBER 5, MAY, 1950

Para-aminosalicylic Acid Treatment in Pulmonary Tuberculosis. Comparison between 94 Treated and 82 Untreated Cases. THE THERAPEUTIC TRIALS COMMITTEE OF THE SWEDISH NATIONAL ASSOCIATION AGAINST TUBERCULOSIS 597
Para-aminosalicylic Acid (PAS) in Pulmonary and Extrapulmonary Tuberculosis. BO CARSTENEN 613
Para-aminosalicylic Acid Therapy in Intestinal Tuberculosis. IVAR KÄLLQVIST 621
Febrile Reactions to Para-aminosalicylic Acid. JULIA R. DAVIN AND ARTHUR E. T. ROGERS 643
Spread or Exacerbation of Pulmonary Tuberculous Lesions as a Result of Thoracoplasty. STEPHEN C. H. YANG AND WILLIAM M. LEES 648
Tuberculous Empyema: Clinical Course and Management. With a Review of 146 Cases. JAMES CUTHBERT 662
Air Evacuation of Tuberculous Military Patients. WILLIAM H. ROPER AND JAMES J. WARING 678
Laboratory Diagnosis of Pulmonary Mycoses. NORMAN F. CONANT 690
Susceptible, Resistant, and Dependent Tubercle Bacilli Isolated from Patients Treated with Streptomycin. CORA RUST OWEN, JOHN ADCOCK, ROBERT M. STOW, LOUIS W. STAUDT, AND WINTHROP N. DAVEY 705
Streptomycin-resistant Tubercle Bacilli. Incidence in Cases Treated with Different Dosage Schedules. WILLIAM E. DYE 719
Duplication of Roentgenograms by Artificial Solarization. With Emphasis on a Simple Standardized Technique. WILLIAM H. ROPER 725
Bacteriostatic and Bactericidal Effects of Products of Sarcoid Lymph Nodes on the Tubercle Bacillus. SOL ROY ROSENTHAL 730

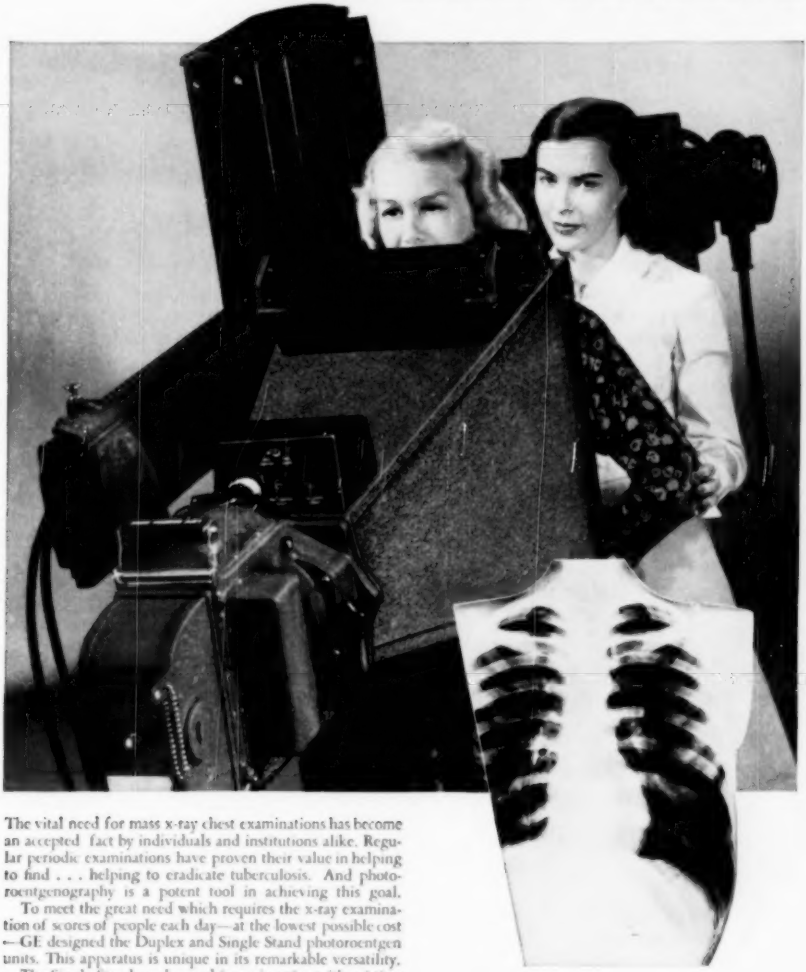
The Effect of Antihistaminic Drugs upon the Tuberculin Reaction. MILTON GRAUB AND ELLIS M. BARRIST 735
Kojic Acid as an Inhibitor of Tubercle Bacilli. HENRY F. LEE, BEN BOLTJES, AND WILLIAM EISENMAN 738
Case Reports:
Emphysematous Bulla Complicated by Hemorrhage and Infection. Treated with Surgical Drainage. WILSON WEISEL AND IRVIN SLOTNIK .. 742
Streptomycin and Promizole in the Treatment of Widespread Pulmonary Tuberculosis in a 19-day-old Infant. Case Report. EDWIN L. KENDIG, JR. AND FRANKLIN L. ANGELL 747
Editorial: Scientific Appraisement of New Drugs in Tuberculosis. MARC DANIELS 751
Books 757
American Trudeau Society: Report of the Subcommittee on Clinical Classification of the Committee on Revision of Diagnostic Standards 760
Abstracts 85

NUMBER 6, JUNE, 1950

An Evaluation of the Method of Quantitative Airborne Infection and its Use in the Study of the Pathogenesis of Tuberculosis. MAX B. LURIE, A. G. HEPPLESTON, SAMUEL ABRAMSON, AND IRENE B. SWARTZ 765
Extraction of Proteins and Other Constituents from the Tubercle Bacillus, with Some Observations on Their Chemical and Biological Properties. ROBERT J. HECKLY AND DENNIS WATSON 798
The Results of the Treatment of Active Minimal Pulmonary Tuberculosis with "Modified" Bed Rest. A Statistical Analysis of 289 Patients Followed for Seven Years after Discharge from Trudeau Sanatorium. ROGER S. MITCHELL AND JACK R. KNUDSON 809
Incidence and Significance of Thromboembolism in Pulmonary Tuberculosis. RUSSELL S. JONES, THOMAS C. BLACK, AND HAROLD A. SPARR ... 826
The Occurrence of Pulmonary Tuberculosis following Pulmonary Excision for Nontuberculous Disease. HARRY LEON KATZ 835
Pleural, Peritoneal, and Pericardial Tuberculosis: A Review of 209 Cases Uncomplicated by Treatment or Secondary Infection. OSCAR AUERBACH 845
Influence of *p*-(Di-n-Propylsulfamyl)-Benzoic Acid, "Benemid", on Para-aminosalicylic Acid (PAS) Plasma Concentrations. WILLIAM P. BOGER AND FORREST W. PITTS 862
Tuberculous Patients Two and a Half Years after Streptomycin Treatment. M. MAXIM STEINBACH, GEORGE C. LEINER, ABRAHAM A. POLACHEK, AND PAUL HELLER 868
Aureomycin in the Treatment of Tuberculosis. W. S. SCHWARTZ, S. T. WALTON, AND R. E. MOYER 875
Case Reports:
Tuberculous Infection with Streptomycin-resistant Organisms. L. S. ARANY AND W. G. LEWIS 881

Spontaneous Mediastinal Emphysema and Bilateral Spontaneous Pneumothoraces. BERNARD HYDE AND LEROY HYDE 883
Primary Coccidioidomycosis and Comcomitant Tuberculosis. MARCEL KAHN 887
Editorial: Implications of Rapidly Effective Tuberculosis Therapy. FLOYD FELDMANN 892
Letters to the Editors: Serum Gamma-Globulins in Pulmonary Tuberulosis. MAURICE J. SMALL 893
Books 895
Index of Subjects and Authors 899
Index of Abstracts 105

An ideal answer for faster
T. B. CASE FINDING



The vital need for mass x-ray chest examinations has become an accepted fact by individuals and institutions alike. Regular periodic examinations have proven their value in helping to find . . . helping to eradicate tuberculosis. And photoroentgenography is a potent tool in achieving this goal.

To meet the great need which requires the x-ray examination of scores of people each day—at the lowest possible cost—GE designed the Duplex and Single Stand photoroentgen units. This apparatus is unique in its remarkable versatility.

The Single Stand can be used in conjunction with existing diagnostic facilities, while the Duplex model is a complete x-ray unit in itself . . . making possible the selection of a particular combination to meet the specific need!

For illustrated information about these photoroentgen units, see your local GE representative, or write General Electric X-Ray Corporation, Dept. **S-6,** Milwaukee 14, Wis.

GENERAL ELECTRIC
X-RAY CORPORATION

EUDOWOOD SANATORIUM
Towson, Maryland

A modern, thoroughly equipped institution for the treatment of tuberculosis. Located on a large 350-acre farm in the beautiful, healthful Maryland countryside. All city conveniences . . . eight miles north of Baltimore . . . one mile east of Towson, Maryland.

Private rooms with adjoining baths . . . $7.00 and $10.00 per day, including general nursing and medical attention. *For further information, address:*

DR. WILLIAM A. BRIDGES, *Superintendent*
Eudowood, Towson 4, Maryland

Streptomycin and Dihydrostreptomycin in Tuberculosis

Edited by H. McLEOD RIGGINS, M.D. and H. CORWIN HINSHAW, M.D.
554 pages X-ray reproductions Cloth cover $7.50

This timely volume will provide, for the first time, detailed information covering the use of streptomycin in the treatment of tuberculosis. In 9 sections and 34 authoritative reports, these specific data are assembled:

Summary of early experimental and clinical studies.

Analysis of bacteriological problems, with emphasis on the sensitivity of the tubercle bacillus to streptomycin.

Pathology of tuberculosis in relation to chemotherapy.

Ten papers reporting methods and results of the special investigation by the American Trudeau Society's Committee on Chemotherapy, experience with several hundred patients, including explicit data on dosages, regimens, therapeutic results, and toxic effects.

Tabular and graphic summary of the combined clinical data.

Preliminary report of the Veterans Administration Streptomycin Committee.

Special articles on toxic manifestations and the streptomycin treatment of bone and joint tuberculosis and tuberculosis of the genitourinary tract.

Dihydrostreptomycin, experimental and clinical studies.

Studies in combined chemotherapy, with emphasis on the role of PAS.

NATIONAL TUBERCULOSIS ASSOCIATION · 1790 Broadway, New York, N. Y.

The Protein-Rich Breakfast and Morning Stamina

Extensive studies* by the Bureau of Human Nutrition have established that breakfasts rich in protein and supplying 500 to 700 calories, effectively promote a sense of well-being, ward off fatigue, and sustain blood sugar levels at normal values for the entire morning postbreakfast period.

These physiologic advantages are related mainly to the protein content rather than to the caloric content of the breakfast. In fact, when isocaloric breakfasts were compared, those with the higher amounts of protein led to the greatest beneficial effects. Breakfasts providing the lower quantities of protein (7 Gm., 9 Gm., 16 Gm., and 17 Gm. respectively) produced a rapid rise in the blood sugar level and a return to normal during the next three hours. Breakfasts providing more protein (22 Gm. and 25 Gm. respectively) produced a maximal blood sugar rise which was lower than that following the breakfasts of lower protein content, but the return to normal was delayed beyond the three hour period.

The subjects on the higher protein breakfasts "reported a prolonged sense of well-being and satisfaction." The findings indicated that the beneficial effects of the high protein breakfast on the blood sugar level may extend into the afternoon.

Meat, man's preferred protein food, is a particularly desirable means of increasing the protein contribution of breakfast. The many breakfast meats available are not only temptingly delicious and add measurably to the gustatory appeal and variety of the morning meal, but they also provide biologically complete protein, B-complex vitamins, and essential minerals. *Meat for breakfast, a time-honored American custom, is sound nutritional practice.*

*Orent-Keiles, E., and Hallman, L. F.: The Breakfast Meal in Relation to Blood-Sugar Values, Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

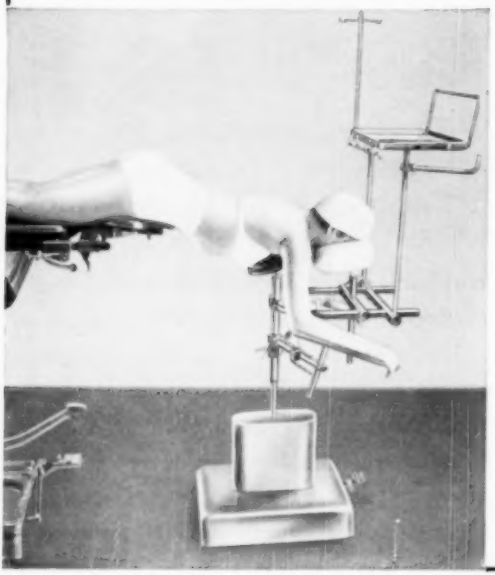
The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

American Meat Institute

Main Office, Chicago...Members Throughout the United States

The NACLERIO SUPPORT *for*

Prone-Position Surgery



used in conjunction with any standard operating table, to keep maximum vital capacity, minimize mediastinal shift, prevent contralateral spillage, and provide ideal access for surgery, with all favorable variations of the patient's position.

SIMPLE—INEXPENSIVE—PORTABLE—VERSATILE

Write for Circular

J. H. EMERSON CO.

22 COTTAGE PARK AVENUE
CAMBRIDGE 40, MASSACHUSETTS

Makers of
EMERSON LUNG IMMOBILIZERS

OAK RIDGE SANATORIUM

GREEN SPRINGS, OHIO

for TUBERCULOSIS

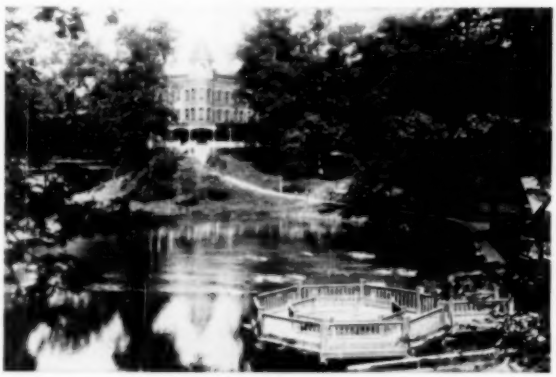
•

Diagnosis
Treatment

•

SITUATED in the beautiful springs country of Northern Ohio, this modern Sanatorium offers not only up-to-date treatment for all forms of Tuberculosis but a setting of utmost beauty and restfulness for the convalescent. General Hospital Facilities with complete Surgery . . . Modern Steam-heated Rooms . . . Graduate Nurses . . . Personal Care for Every Patient.

Natural Mineral Spring
(8,000,000 gallons per day.)
Artesian Well



Reasonable rates

PAUL M. HOLMES, M.D., Medical Director
JOHN J. GEDERT, M.D., Resident Physician
GEO. S. BOWERS, M.D., Internist
ELEANOR BLIVEN, R.N., Supt. Nurses
ALEX C. JOHNSON, Pres. & Gen. Mgr.
M. M. RIDDLE, M.D., Eye, Ear, Nose and Throat
WM. NEILL, M.D., Thoracic Surgeon
OTTO MUHME, M.D., Thoracic Surgeon

70mm FLUORO-RECORD CUT FILM CAMERA

LEADING HEALTH AUTHORITIES suggest routine chest x-rays for all hospital admissions and hospital personnel as a positive aid in detecting and checking the spread of tuberculosis. And leading radiologists endorse the use of inexpensive, easy-to-use 70mm cut film for this purpose because it can be processed immediately after exposure for quick interpretation and is convenient for filing.

The Fairchild 70mm Fluoro-Record Cut Film Camera provides two individual x-rays or a stereo pair on a single sheet of 6½ x 2-11/16 inch cut film. Negative sizes may be 2½ x 2½ inches or 2½ x 3 inches. Spring-loaded shift release mechanism positions 2-exposure cut film holder accurately for each exposure either manually or electrically by remote control. This camera can be obtained on new photo x-ray units of leading manufacturers or adapted for use with many types of existing equipment.

For details see your x-ray equipment supplier or write to Dept. CS, 88-06 Van Wyck Boulevard, Jamaica 1, N. Y.

Other Fairchild precision x-ray equipment includes the new Roll Film Cassette for angiographic studies; 70mm roll film cameras for mass chest x-rays; 70mm cut film and roll film viewers; 70mm film processing equipment; and Chamberlain X-Ray Film Identifier.

Fairchild
CAMERA AND INSTRUMENT CORPORATION

SCHENLEY LABORATORIES

announces the availability of

TIBIONE

brand of 4-acetylaminobenzal thiosemicarbazone

a new antimicrobial agent for tuberculosis

developed by DRS. DOMAGK, SCHMIDT, BEHNISCH, and MIETZSCH of the BAYER LABORATORIES at Leverkusen and Elberfeld, Western Zone of Germany

Known abroad as TB1/698, TIBIONE has been used in treating more than 7,000 tuberculosis patients in Europe and is now being extensively studied by leading tuberculosis groups in the United States, using material supplied by Schenley Laboratories, sole American licensee. Clinicians and institutions desiring to purchase TIBIONE for use in clinical investigation under F & D A regulations are invited to communicate directly with the Medical Director of Schenley Laboratories.

SCHENLEY LABORATORIES, INC.

350 Fifth Avenue, New York 1, N. Y.

© Schenley Laboratories, Inc.

ALUM ROCK SANATORIUM

SAN JOSE, CALIFORNIA

Telephone CLayburn 8-4921

A non-profit sanatorium for the treatment of Tuberculosis and other diseases of the chest.

Medical Director
Buford H. Wardrip, M.D.
Associate Medical Director
C. G. Scarborough, M.D.

Visiting Medical Staff:

Harold Gayon Trimble, M.D., Oakland
Cabot Brown, M.D., San Francisco
Gerald L. Crenshaw, M.D., Oakland
J. Lloyd Eaton, M.D., Oakland
Ira Gourley, M.D., Oakland
H. Corwin Hinshaw, M.D., San Francisco
Glenroy N. Pierce, M.D., San Francisco
James Robert Wood, M.D., Oakland

A SPECIAL ANNOUNCEMENT TO SUBSCRIBERS

For more than five years, the American Review of Tuberculosis has been waging a losing battle against advancing production costs. The prices of paper, type-setting, presswork, and binding have steadily mounted, and the end is not yet in sight.

With reluctance, therefore, we are forced to announce an increase in the subscription rate from $8.00 to $10.00, *effective January 1950.*

THE AMERICAN REVIEW OF TUBERCULOSIS
1790 Broadway, • New York, N. Y.

Present Concepts of Rehabilitation in Tuberculosis

by NORMAN C. KIEFER, M.D.

420 pages, cloth cover $3.50

In this volume there is brought together, for the first time, an accurate summary of world research and achievement in every area of rehabilitation during the last decade.

More than 1,000 original papers are abstracted in this book, and in every case the salient features of each have been brought together in classified sections to provide a complete picture of approaches, procedures, and results.

A bibliography of more than 1,000 items supplies reference to basic sources, and a particularly comprehensive index facilitates the location of specific information.

Your order can be filled promptly.

NATIONAL TUBERCULOSIS ASSOCIATION
1790 Broadway, New York 19, N. Y.

Maryknoll SANATORIUM

(Maryknoll Sisters)

MONROVIA, CALIFORNIA

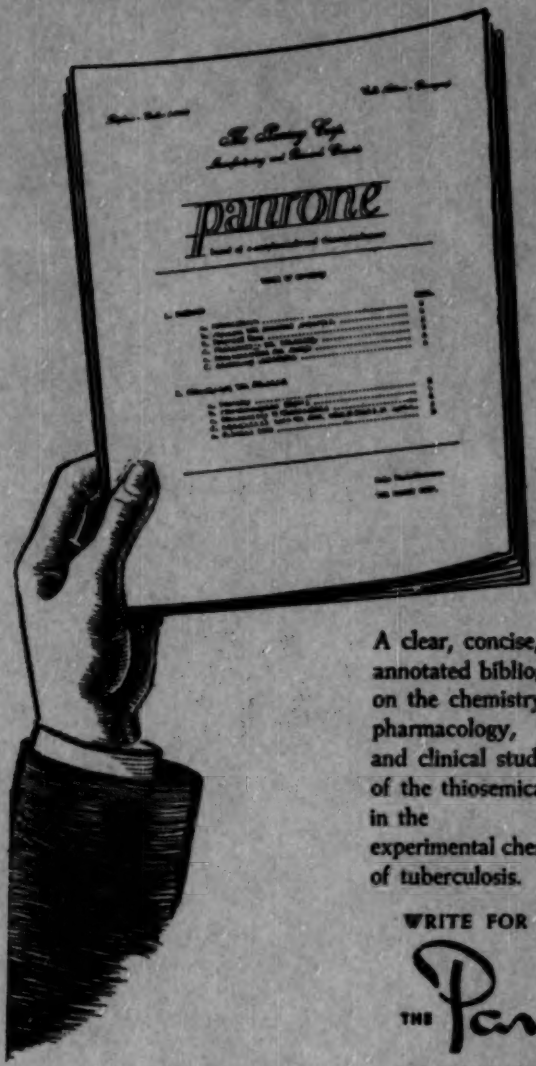
• A Sanatorium for the treatment of tuberculosis and other diseases of the lungs. Located in the foothills of the Sierra Madre Mountains, Southern exposure. Accommodations are private, modern, and comfortable. Rates are moderate. General care of patient is conducive to physical and mental well being.

SISTER MARY PIETA
Superintendent

E. W. HAYES, M.D.
Medical Director

Now Available...

PANRONE LITERATURE



A clear, concise,
annotated bibliography
on the chemistry,
pharmacology,
and clinical studies
of the thiosemicarbazones
in the
experimental chemotherapy
of tuberculosis.

WRITE FOR YOUR COPY TODAY.

THE Panray CORP.
340 CANAL STREET, NEW YORK 13, N. Y.

CUSTOM MANUFACTURERS OF FINE MEDICINAL CHEMICALS